Efficacy and Safety of the α_7-Nicotinic Acetylcholine Receptor Agonist ABT-126 in the Treatment of Cognitive Impairment Associated With Schizophrenia:

Results From a Phase 2b Randomized Controlled Study in Smokers

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ABSTRACT

Objective: To evaluate the efficacy and safety of the α_7-nicotinic receptor agonist ABT-126 for treatment of cognitive impairment in stable subjects with schizophrenia who smoke.

Methods: A 12-week double-blind, placebo-controlled, parallel-group study was conducted from August 2012 to March 2014. Subjects with a diagnosis of schizophrenia based on *DSM-IV-TR* criteria (confirmed by the Mini-International Neuropsychiatric Interview version 6.0.0) were randomized 1:1:1 to ABT-126 25 mg, ABT-126 75 mg, or placebo once daily while maintained on their background antipsychotic medication. The primary endpoint was the change from baseline on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) neurocognitive composite score; the primary analysis compared ABT-126 with placebo at week 12 using a mixed-effects model for repeated measures. Secondary endpoints included the change from baseline on the University of California San Diego Performance-based Skills Assessment-2 Extended-Range, the 16-item Negative Symptom Assessment scale (NSA-16), and safety assessments.

Results: Of the 157 randomized subjects, 82% completed the study. The mean baseline MCCB neurocognitive composite score for the entire study sample was 28.8; scores were similar across groups. No statistical difference in the change from baseline score between any of the ABT-126 dose groups and placebo was observed on the MCCB neurocognitive composite score (ABT-126 25 mg, +0.28; ABT-126 75 mg, +0.41; placebo, +1.42). Differences in the NSA-16 total score were seen with ABT-126 75 mg versus placebo at week 6 (−2.79; $P = .011$) and week 12 (−1.94; $P = .053$). Adverse events with ABT-126 were similar to placebo, except for constipation (5.8% for ABT-126 vs 0% for placebo).

Conclusions: ABT-126 did not demonstrate a procognitive effect in subjects with stable schizophrenia who smoke. A trend for improvement in negative symptoms was observed with the high dose. The safety profile of ABT-126 was similar to placebo.

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Cognitive impairment substantially limits the ability of patients with schizophrenia to function in the community.[1,2] These limitations are manifested in lower rates of education, employment, home ownership, and personal relationships. Despite the lifetime impact of cognitive impairment in patients with schizophrenia, no medications are approved to treat this symptom domain. The only known effective treatment is cognitive remediation, a therapy with a relatively modest effect size (approximately 0.45) requiring considerable and persistent effort by patients and providers.[3] Several classes of pharmacologic agents, including histamine-3 antagonists,[4–6] cannabinoid-1 and cannabinoid-2 antagonists,[7] γ-aminobutyric acid A α_2/α_3 partial agonists,[8] and $\alpha_4\beta_2$- and α_7-nicotinic receptor agonists,[9–13] have been studied, but none have been successful in phase 3 pivotal studies to date. The α_7-nicotinic receptor agonists have shown procognitive effects in schizophrenia. The prototype DMXB-A/GTS-21 has demonstrated significant improvements on the Repeatable Battery for the Assessment of Neuropsychological Status in patients with schizophrenia.[13] Efficacy has also been reported with RG3487/MEM3454,[14] TC-5619,[12] and EVP-6124/encenicline.[9] The early successes of RG3487[11] and TC-5619[15] were not recapitulated in subsequent studies,[11] but the other agents remain under investigation.

We previously reported results of a phase 2 US study with ABT-126, a potent and selective α_7-nicotinic receptor partial agonist.[16] The effect of ABT-126 on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognition Battery (MCCB)[17,18] approached significance in the intent-to-treat (ITT) population. When effect of ABT-126 was analyzed by smoking status, there appeared to be an effect (Cohen *d* effect size > 0.8) in the nonsmoker (approximately 40%) subgroup of the population and no effect in the population of current smokers. The disparate effects based on smoking status were not unanticipated. Some investigators have excluded subjects who smoke from studies of nicotinic agonists, and others have restricted smoking around the time of cognition testing in such studies; our study permitted ad libitum smoking.

The majority of patients with schizophrenia smoke. Smoking has been suggested to be an attempt at self-medication for cognitive impairment, positive symptoms, or side effects of medication[19] and to alter neuropsychological outcomes in schizophrenia.[20] Indeed, Segarra et al[19] reported greater baseline

cognitive performance among smokers versus nonsmokers with schizophrenia, but only the nonsmokers experienced significant improvements in cognitive measures during antipsychotic treatment. Any cognitive benefit obtained from nicotine via smoking is likely to be obscured due to tachyphylaxis. Our previous study found virtually identical baseline MCCB scores in smokers and nonsmokers.[16] In regard to treatment with a nicotinic agonist, lack of improvement in smokers could relate to an interaction with nicotine at the α_7 receptor.[21]

Post hoc analyses of results from the previous phase 2 study also suggested a possible inverse relationship between the number of cigarettes smoked daily and the procognitive effect as measured by the MCCB as well as potential correlations between the procognitive effect in smokers and different single nucleotide polymorphisms on the catechol-*O*-methyltransferase (*COMT*) gene (G.M.H., data on file, 2014).

Despite the lack of procognitive effects seen at the 25-mg dose in the smoking population, this study was conducted to further evaluate the negative findings in this population by investigating whether higher doses of ABT-126 may overcome receptor desensitization and determining if a subset of the smoking population (ie, light smokers) would respond to ABT-126.

Clinical Points

- Patients with schizophrenia struggle with cognitive impairment throughout their lifetime, which limits their ability to function in the community.
- Several drug classes have been investigated as potential treatment options for cognitive impairment in patients with schizophrenia, yet no drugs have been approved to treat this symptom domain.
- A potent and selective α_7-nicotinic receptor partial agonist, ABT-126, did not demonstrate a procognitive treatment effect in patients with schizophrenia who were smokers.

METHODS

Study Design

This randomized, double-blind, placebo-controlled, parallel-group study evaluated the efficacy and safety of ABT-126 in treating cognitive impairment associated with schizophrenia in subjects who were clinically stable, smoked regularly, and were receiving an antipsychotic regimen. The study was designed and conducted in accordance with the MATRICS guidelines[22,23] at 20 sites in the United States from August 2012 to March 2014. Approval from institutional review boards and written informed consent were obtained prior to any study procedures.

Subjects were screened for eligibility at 2 visits within 4 to 6 weeks of randomization. Randomization was planned for 150 subjects (50 per group) in a 1:1:1 ratio to receive ABT-126 25 mg, ABT-126 75 mg, or matching placebo orally once daily for 12 weeks. Subjects were randomized via an interactive voice-response/web-based system based on a randomization schedule provided by the sponsor. Randomization was stratified by site and genotype on the rs4818 single nucleotide polymorphisms of the *COMT* gene, with strata for minor allele carriers (G/G or G/C genotypes) and for major allele homozygotes (C/C genotype only). Assessments occurred at weeks 1, 2, 4, 6, 8, 10, and 12 during the treatment period and a 14-day follow-up visit after the last dose of study drug.

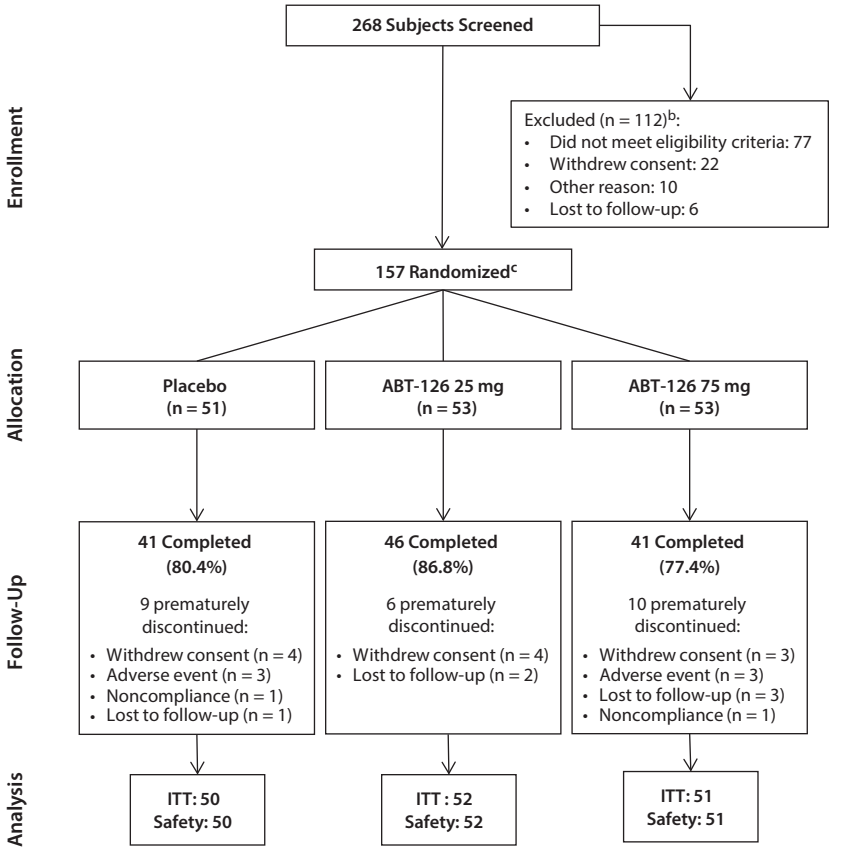
Subjects

Clinically stable subjects 20 to 65 years old were eligible if they had a diagnosis of schizophrenia based on *DSM-IV-TR* criteria (confirmed by the Mini-International Neuropsychiatric Interview version 6.0.0[24]). A diagnosis of schizophrenia with treatment for ≥ 2 years was required. Clinical stability was defined as no psychiatric inpatient hospitalization or destabilization within the previous 4 months; a regimen of antipsychotic medications, mood stabilizers, and antidepressants that remained stable for 8 weeks prior to treatment; and core positive symptoms of no worse than moderate severity.

Subjects were to be in general good health as determined by medical history, physical examination, 12-lead electrocardiograms (ECGs), and laboratory testing. Participants were regular cigarette smokers for ≥ 3 months with positive cotinine test results at screening and no plans to quit smoking during the study. Most marketed antipsychotics were permitted, with the exceptions detailed in the next paragraph.

Major exclusion criteria included significant neurologic disease; a positive urine drug screen; recent evidence of significant suicidality or violent ideation; current major depressive episode (based on the Calgary Depression Scale for Schizophrenia[25]); hepatitis B or C or HIV infection; body mass index > 45 kg/m^2 or body weight > 145 kg; history of substance abuse (within 6 months prior to screening visit 1, met the *DSM-IV-TR* criteria for a substance dependence disorder and had not remitted for at least 1 year prior to screening visit 1, or could interfere with the conduct of the study); uncontrolled mental illness; seizures; current participation in cognitive remediation training; or participation in another trial utilizing the University of California Performance-Based Skills Assessment (UPSA, any version) within the previous 6 months. A history or risk factors for torsades de pointes, an abnormal ECG, or prolongation of the QT interval corrected (QTc) for heart rate using the Fridericia formula (QTcF > 450 ms for men or > 470 ms for women) at the first screening visit were also exclusion criteria. Most of the currently available atypical antipsychotic medications and many conventional agents were permitted. Medications associated with torsades de pointes, mood stabilizers, sertindole, iloperidone, chlorpromazine, pimozide, thioridazine, citalopram (> 20 mg daily), bupropion, highly anticholinergic tricyclic antidepressants, and monoamine oxidase inhibitors were prohibited. Clozapine was excluded except when it was used at a low dose (≤ 100 mg) for sleep.

Figure 1. Subject Disposition[a]



[a]The primary reason for discontinuation is provided for subjects who prematurely discontinued.
[b]Subjects could have more than 1 reason for exclusion.
[c]4 Subjects were randomized but did not take study drug (placebo, n = 1; ABT-126 25 mg, n = 1; and ABT-126 75 mg, n = 2).
Abbreviation: ITT = intent to treat.

Primary Efficacy

The MCCB[17,18] was conducted during screening, on the day prior to the first dose (baseline), and at weeks 6 and 12. The MCCB has shown good test-retest reliability, discriminates patients with schizophrenia from healthy subjects, and correlates with functional status.[17,18] Alternate versions of verbal learning, visual learning, and reasoning were to be used to minimize practice effects. The primary endpoint was the change from baseline on the MCCB neurocognitive composite score (all domains except social recognition) compared with placebo at week 12. The primary efficacy variable was changed from the MCCB composite score to the MCCB neurocognitive composite score via a protocol amendment. The change was a result of findings from a previous study,[16] which indicated that the MCCB neurocognitive composite score had greater sensitivity to ABT-126 treatment effects. Scoring of the MCCB is based on a normative distribution (T-scores), based on a mean ± SD score of 50 ± 10 in a healthy population. All MCCB raters were trained and certified by an experienced external vendor, and each test was reviewed during the trial for scoring accuracy by 2 independent experts employed by the vendor. Scoring discrepancies were reconciled with the rater.

Secondary Efficacy

Secondary endpoints included the change from baseline on the MCCB composite score and individual domain scores, the UPSA-2 Extended Range total score (UPSA-2ER; conducted at baseline and week 12), and the 16-item Negative Symptom Assessment scale total score (NSA-16; baseline, weeks 6 and 12).[26] The UPSA-2ER is a modified version of the UPSA-2[27] created for the current study. The UPSA-2ER retains the original domains of the UPSA-2 with more difficult items added to each domain to make it more challenging and reduce possible ceiling effects. The NSA-16 is a 16-item instrument plus a 1-item global rating designed to measure the severity of specific negative symptoms in schizophrenia. Clinical symptoms were evaluated at baseline and at weeks 6 and 12 using the Positive and Negative Syndrome Scale (PANSS)[28] and the Clinical Global Impressions–Severity of Illness scale (CGI-S).[29] The Modified Tobacco Craving Questionnaire–Short Form (MTCQ-SF)[30] was administered to evaluate cigarette

Table 1. Baseline Characteristics (safety dataset, N = 153)[a]

Demographic Characteristic	Placebo (n = 50)	ABT-126 25 mg (n = 52)	ABT-126 75 mg (n = 51)
Age, mean (SD), y	43.5 (10.02)	45.7 (8.69)	44.2 (10.97)
Sex			
Male	41 (82.0)	40 (76.9)	40 (78.4)
Female	9 (18.0)	12 (23.1)	11 (21.6)
Race			
Black	29 (58.0)	30 (57.7)	28 (54.9)
White	18 (36.0)	19 (36.5)	21 (41.2)
All other[b]	3 (6.0)	3 (5.8)	2 (3.9)
Cigarette use, mean (SD), y	21.8 (12.28)	21.4 (12.28)	19.1 (11.95)
Cigarettes/d in last week, mean (SD)[c]	14.26 (8.94)	16.05 (10.57)	14.26 (6.93)
Cigarettes/d			
> 10	24 (48.0)	30 (57.7)	26 (51.0)
≤ 10	26 (52.0)	22 (42.3)	25 (49.0)
> 20	6 (12.0)	7 (13.5)	4 (7.8)
COMT SNP genotype			
Major allele homozygote	22 (44.0)	24 (46.2)	21 (41.2)
Minor allele homozygote	28 (56.0)	28 (53.8)	30 (58.8)
Psychiatric history			
Years since schizophrenia diagnosis, mean (SD)	18.3 (10.98)	20.6 (9.82)	18.1 (10.25)
No. of prior psychiatric hospitalizations in last 2 years			
0	29 (58.0)	37 (71.2)	30 (58.8)
1	13 (26.0)	8 (15.4)	15 (29.4)
2	7 (14.0)	4 (7.7)	4 (7.8)
3	0	3 (5.8)	1 (2.0)
4	1 (2.0)	0	1 (2.0)
≥ 5	0	0	0

[a]Values shown as n (%) unless otherwise noted.
[b]Includes multirace, Hawaiian native, American Indian/Alaska native, and Asian.
[c]Intent-to-treat dataset.
Abbreviations: *COMT* = catechol-*O*-methyltransferase, SD = standard deviation, SNP = single nucleotide polymorphism.

craving. Nicotine and alcohol use were self-reported by subjects throughout the study.

Safety, Tolerability, and Pharmacokinetics

Physical examinations, clinical laboratory tests, 12-lead ECGs, and vital signs were conducted regularly, and adverse events were reported and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 (www.meddra.org). Investigators determined the severity (mild, moderate, severe) of adverse events and relationship to study drug (reasonable possibility or no reasonable possibility). The Columbia Suicide-Severity Rating Scale[31] was administered at weekly visits, and the Physician Withdrawal Checklist-20[32] was administered at the end of the follow-up period. Extrapyramidal symptoms were evaluated using the Abnormal Involuntary Movement Scale,[29] Barnes Akathisia Scale,[33] and Simpson-Angus Scale[34] at baseline and weeks 2 and 10.

Subjects' compliance with treatment was evaluated regularly by capsule counts. In addition, pharmacokinetic sampling was done at baseline and at weeks 1, 2, 4, 6, 8, and 12. The sponsor determined plasma ABT-126 concentrations using a validated liquid chromatography/mass spectrometry method at the conclusion of the study. Pharmacokinetic results were also utilized to assess medication compliance.

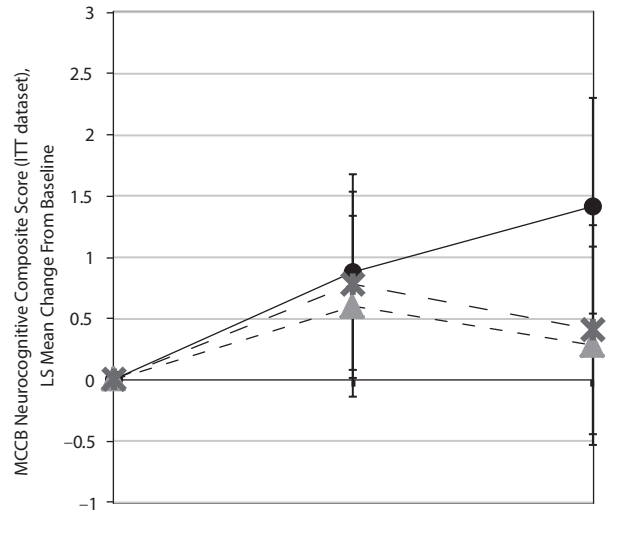
Statistical Analysis

Because this study was designed to initially evaluate the potential efficacy of a high and a low dose of ABT-126 versus placebo in smokers, the sample size for a fixed level of power was not determined. However, a sample size of 50 per group had 80% power to detect an effect size of 0.53 using a 1-sided test with a type I error rate of 5%, assuming 10% of subjects lacked post-randomization data. Efficacy analyses were conducted on the ITT dataset, defined as randomized subjects who took ≥ 1 dose of study drug and had ≥ 1 efficacy measurement, including baseline. The primary efficacy analysis was a likelihood-based, mixed-effects model, repeated measures (MMRM) analysis of the change in the MCCB neurocognitive composite score from baseline to each subsequent assessment up to and including week 12. The model included fixed, categorical effects for treatment, site, visit, and treatment-by-visit interaction, with continuous fixed covariates for baseline score and the baseline score–by-visit interaction. The treatment effect on the primary efficacy endpoint was first analyzed by an analysis of covariance (ANCOVA) model with factors of treatment, site, *COMT* rs4818 genotype (G/G or G/C vs C/C genotype), and treatment-by-genotype interaction and with baseline scores as a covariate. If the treatment-by-genotype interaction *P* value was ≤ .30 (2-sided test), genotype subsets were to be analyzed with an MMRM analysis.

Secondary analyses on the primary efficacy variable were performed on the ITT dataset using an ANCOVA model with factors of treatment and site and with baseline score as a covariate on change from baseline to the final evaluation of MCCB. The secondary efficacy variables of composite and 7 domain scores of the MCCB, NSA-16 total and subscale scores, PANSS total and subscale scores, CGI-S scores, and MTCQ-SF scores were analyzed by an MMRM analysis as described for the primary endpoint; UPSA-2ER total and subscale scores were analyzed using the ANCOVA model. Treatment comparisons were performed using 1-sided tests at the significance level of 0.050, and no multiplicity adjustment was performed.

Additional prespecified subgroup analyses for the MCCB change from baseline to last observation were conducted to examine the impact on response to treatment of the following factors: sex, age, number of cigarettes daily (light smoking defined as ≤ 20 cigarettes per day by self-report), baseline serum cotinine level (≤ median or > median), baseline MCCB neurocognitive composite score (≤ median or > median), baseline PANSS Marder positive/negative factor score (mean of PANSS Marder negative factor 7 scores greater than or less than the mean of PANSS Marder positive factor 8 scores), anticholinergic activity of background antipsychotic medications,

Figure 2. LS Mean Change From Baseline in MCCB Neurocognitive Composite Total Score[a]



No. of subjects:			
Placebo	44	43	39
ABT-126 25 mg	49	48	45
ABT-126 75 mg	46	46	41

Placebo — ABT-126 25 mg — ABT-126 75 mg

[a]An increase in score indicates improvement. Error bars represent the standard error of the LS mean. There were no statistically significant 1-sided *P* values from the repeated-measures model. The model included treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure was unstructured.

Abbreviations: ITT = intent to treat, LS = least squares, MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia, MCCB = MATRICS Consensus Cognitive Battery.

duration of schizophrenia diagnosis (< 10 years or ≥ 10 years), and study site. A baseline PANSS Marder positive/negative factor scores subgroup analysis was also conducted for the NSA-16 total score change from baseline to last observations. Safety analysis statistical tests were 2-tailed at α = .050, if applicable.

RESULTS

Subject Disposition and Baseline Characteristics

A total of 157 subjects were randomized, and 83.7% completed the study; 4 randomized subjects did not take study drug (Figure 1). Overall, 79.1% were male, 56.9% were black, and the mean (SD) age was 44.5 (9.91) years. Subjects had smoked a mean of approximately 15 cigarettes per day for a mean (SD) duration of 20.7 (12.15) years. The most frequently reported concomitant antipsychotic medications were risperidone (35.3%), quetiapine (26.8%), haloperidol (13.1%), aripiprazole (12.4%), and olanzapine (12.4%). Key baseline characteristics are presented in Table 1. No statistically significant differences among the treatment groups were observed in baseline demographic characteristics, psychiatric history, or cigarette use. Subjects maintained a similar level of smoking throughout the study. Eighteen randomized subjects were excluded from the primary analysis: 14 subjects were missing postbaseline MCCB neurocognitive composite score, and 4 subjects did not take study drug.

Study Medication Compliance

Based on capsule counts, 86.9% of subjects were considered compliant with study drug, and overall compliance was > 94% for each week of the study. No significant differences among treatment groups were observed for overall compliance, compliance at any time point, or duration of exposure. Observed mean plasma ABT-126 concentrations at each dose level were consistent with predicted values determined from previous ABT-126 studies.

Efficacy

The treatment-by-genotype interaction *P* value from the ANCOVA model did not reach the prespecified level of significance (2-sided $P \leq .3$), so the primary efficacy analysis was conducted in ITT subjects without stratification by *COMT* rs4818 genotype. No significant differences were observed in the primary MMRM analysis for either dose of ABT-126 versus placebo on the mean change in MCCB neurocognitive composite score from baseline to week 12 (Figure 2). The model-based least-squares mean of the difference between the ABT-126 25 mg treatment group and placebo in the MCCB neurocognitive composite score was −0.28 at week 6 (90% CI, −2.06 to 1.50; $P = .602$) and −1.14 at week 12 (90% CI, −3.11 to 0.83; $P = .830$). Results for ABT-126 75 mg versus placebo were similar: −0.10 at week 6 (90% CI, −1.93 to 1.73; $P = .537$) and −1.01 at week 12 (90% CI, −3.04 to 1.01; $P = .796$; Supplementary eTable 1).

No statistically significant differences were seen between either ABT-126 dose group and placebo on the change from baseline on the MCCB composite score or the UPSA-2ER total score or subscale scores (Table 2). A trend toward significance was seen on the mean change from baseline on the NSA-16 in the ABT-126 75-mg group compared with placebo (−1.94; $P = .053$; Figure 3) at week 12, and significance was observed at week 6 (−2.79; $P = .011$). With the ABT-126 75-mg treatment group, improvement or trend toward improvement was observed on the affect ($P = .013$ at week 6 and $P = .026$ at week 12), social activity ($P = .042$ at week 6), motivation ($P = .085$ at week 6 and $P = .082$ at week 12), and motor retardation ($P = .088$ at week 6) subscale scores and on the global negative symptom rating score ($P = .051$ at week 6 and $P = .071$ at week 12).

Analyses of the PANSS total or positive symptoms scores showed no statistically significant differences between treatment groups (Table 2). Consistent with the NSA-16, effects were observed for the ABT-126 75-mg dose group on the PANSS negative symptoms subscale score ($P = .051$ at week 6 and $P = .088$ at week 12) and the Marder factor negative symptoms score ($P < .001$ at week 6 and

Table 2. Efficacy Results, Analysis of Covariance (ITT population)[a,b]

Assessment	Placebo	ABT-126 25 mg	ABT-126 75 mg
MCCB neurocognitive composite score			
n	44	49	46
Baseline mean (SD)	32.57 (10.33)	28.55 (12.32)	26.02 (10.81)
LS mean change to final (SE)	1.05 (0.85)	0.31 (0.78)	0.27 (0.82)
P		.741	.745
MCCB composite score			
n	44	49	46
Baseline mean (SD)	30.36 (10.55)	26.08 (12.65)	24.52 (11.98)
LS mean change to final (SE)	0.81 (0.80)	0.68 (0.74)	0.45 (0.77)
P		.550	.630
UPSA-2ER total score			
n	41	47	40
Baseline mean (SD)	83.22 (14.04)	78.53 (17.48)	77.63 (16.81)
LS mean change to final (SE)	3.99 (1.61)	3.39 (1.49)	1.93 (1.61)
P		.610	.822
NSA-16 total score			
n	44	49	46
Baseline mean (SD)	42.70 (11.64)	46.43 (12.15)	44.11 (9.01)
LS mean change to final (SE)	−0.83 (0.93)	−1.12 (0.85)	−3.29 (0.91)
P		.604	.984
PANSS total score			
n	44	48	46
Baseline mean (SD)	63.20 (11.21)	64.35 (10.46)	64.54 (13.47)
LS mean change to final (SE)	−2.15 (1.20)	−1.21 (1.12)	−2.25 (1.18)
P		.260	.526
CGI-S score			
n	44	49	46
Baseline mean (SD)	3.34 (0.61)	3.45 (0.77)	3.39 (0.65)
LS mean change to final (SE)	−0.08 (0.08)	−0.18 (0.07)	−0.21 (0.08)
P		.852	.910

[a]*P* values are 1-sided specified a priori.
[b]The MCCB consists of 10 tests of cognitive functioning (Trail Making Test Part A, Brief Assessment of Cognition in Schizophrenia Symbol Coding, Hopkins Verbal Learning Test—Revised Immediate Recall Three Trial Learning, Wechsler Memory Scale, Spatial Span, Letter-Number Span, Neuropsychological Assessment Battery Mazes, Brief Visuospatial Memory Test—Revised, Category Fluency Test Animal Naming, and Continuous Performance Test Identical Pairs) and 7 domains of cognition (Speed of Processing, Verbal Learning, Working Memory, Reasoning and Problem Solving, Visual Learning, Attention/Vigilance, and Social Recognition). The MCCB neurocognitive composite score includes all MCCB tests except Social Recognition.
Abbreviations: CGI-S = Clinical Global Impressions–Severity of Illness Scale, ITT = intent to treat, LS = least squares, MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia, MCCB = MATRICS Consensus Cognitive Battery, NSA-16 = 16-item Negative Symptom Assessment scale, PANSS = Positive and Negative Syndrome Scale, SD = standard deviation, SE = standard error, UPSA-2ER = University of California San Diego Performance-based Skills Assessment-2 Extended Range.

P = .053 at week 12). No treatment effects were observed on the CGI-S (Table 2) and MTCQ-SF (Supplementary eTable 2). No treatment effects were seen in the prespecified subgroup analyses of the primary efficacy endpoint, including amount of smoking. Least-squares mean change from baseline values for the MCCB neurocognitive composite score was 1 point or less in both light and heavy smokers who received ABT-126. Due to the lack of observed treatment effect in the subgroup analyses, no further analyses were conducted to examine the linear relationship of the response using continuous variables.

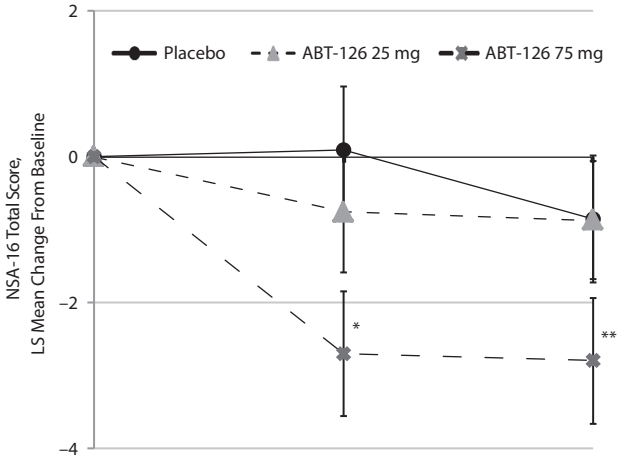
Safety

Adverse events reported by ≥ 2% of all ABT-126–treated subjects combined and at rates greater than placebo were constipation (5.8%); weight increased (5.8%); and dizziness, dyspepsia, fatigue, influenza, tremor, and upper respiratory tract infection (all were 2.9%). Discontinuations due to adverse events and serious adverse events were also similar between treatment groups (Supplementary eTable 3). Rates of schizophrenia exacerbation were similar between treatment groups; 2.9% of ABT-126–treated subjects and 2.0% of placebo-treated subjects experienced adverse events related to psychosis or psychotic disorders. No clinically significant differences were seen between treatment groups in the mean change from baseline in laboratory parameters, vital signs, ECG findings, movement rating scales (Simpson-Angus Scale, Barnes Akathisia Scale, Abnormal Involuntary Movement Scale), or Physician Withdrawal Checklist-20 total score.

DISCUSSION

Our prior study with ABT-126 in a clinically stable population with schizophrenia demonstrated dose-related procognitive effects in nonsmokers and no effect in those

Figure 3. LS Mean Change From Baseline in NSA-16 Total Score[a]



No. of subjects:			
Placebo	44	44	40
ABT-126 25 mg	49	49	46
ABT-126 75 mg	46	46	40

[a]A decrease in the NSA-16 score indicates improvement. Error bars represent the standard error of the LS mean. *P* values are 1-sided from the repeated-measures model with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure was unstructured.
*$P = .011$ vs placebo.
**$P = .053$ vs placebo.
Abbreviations: LS = least squares, NSA-16 = 16-item Negative Symptom Assessment scale.

who currently smoked.[16] Overall, ABT-126 was generally well tolerated in subjects with schizophrenia and exhibited an adequate safety profile to support continued development at higher doses.[16] The rationale for the current study was to further evaluate the results in smokers by investigating a higher dose (up to 75 mg daily) and to assess the relationships between response and the intensity of smoking and *COMT* genotype. In this study, ABT-126 failed to show a procognitive treatment effect in subjects with schizophrenia who were smokers, regardless of dose, substantiating the results of a previous phase 2 study.[16]

In a post hoc analysis of our prior study,[16] a greater effect on cognition was detected in light smokers compared with heavy smokers (G.M.H., data on file, 2014). These findings appeared to support the concept of nicotinic receptor desensitization. The median amount of smoking in both our previous and current studies was approximately one-half pack per day, consistent with epidemiology data indicating trends toward decreasing rates and amounts of smoking among patients with schizophrenia.[35–37] Previous studies with nicotinic agonists have restricted smoking around the time of cognition testing, presumably in an attempt to "resensitize" the receptor and enable a pharmacologic response with the agonist.[13] One might logically conclude that light smoking increases the interval between smoking and cognition testing, thus recapitulating the "resensitization" needed for a pharmacologic effect. We thought this phenomenon occurred in the previous study, which explained the observed effect in light smokers. However, the results of the present study do not support this hypothesis, as there was no evidence of a treatment effect, even in the lightest of smokers. Any hypotheses regarding lower receptor occupancy with α_7 agonists, as some have described,[38] do not appear to be applicable with ABT-126.

The other noteworthy finding from a post hoc analysis in the prior study[16] was the greater procognitive effect demonstrated by subjects with the VAL/MET or MET/MET polymorphism on the *COMT* gene (G.M.H., data on file, 2014). We investigated several single nucleotide polymorphisms, including rs6269, rs4633, rs4680, and rs4818. The results were consistent. The pharmacologic plausibility is that the VAL/MET and MET/MET polymorphisms are associated with slower catabolism of dopamine. We postulated that there would be more dopamine available to the postsynaptic dopamine (presumably D_1) receptor, thus facilitating neurotransmission in the prefrontal cortex.[39] This might be particularly important in the case of an α_7 agonist, with which postsynaptic α_7 receptors are desensitized from chronic nicotine exposure (and presumably not the presynaptic receptor), allowing dopamine to exert an effect in lieu of acetylcholine. Deliberate inhibition of *COMT* has been investigated as a possible procognitive therapeutic strategy, particularly with tolcapone and entacapone in patients with schizophrenia who smoke, but the results are mixed.[40] The lack of effect in this study does not put an end to this question. While we were disappointed that the results from our previous phase 2 studies could not be reproduced, perhaps a study designed to specifically address this question could have provided more encouraging results.

We recently reported[41] that, in a dose-ranging phase 2b study, ABT-126 (25–75 mg) did not demonstrate a consistent effect on cognition in nonsmoking subjects with schizophrenia compared with placebo but did demonstrate a trend toward an effect on negative symptoms. Encouraging results on reducing negative symptoms have been reported with the α_7 agonists RG3487,[11] TC5619,[12] and EVP6124/encenicline.[9] In all cases, negative symptom measures were secondary endpoints in cognition studies, and in the case of TC5619 and RG3487, the effect on negative symptoms was not accompanied by a procognitive effect, supporting the idea that negative symptoms and cognition are separate constructs. In our current study, the various negative symptom endpoint measures were consistent. However, two points with our data might warrant circumspection, the first being the magnitude of the effect. The difference between placebo and the ABT-126 75-mg treatment group at 12 weeks was approximately 2 points, a difference that may not be considered clinically significant. However, improvement was seen on the NSA-16 global negative symptom item, suggesting clinical relevance. Second, when the negative symptom data were analyzed by severity of baseline score

(greater than and less than median), the difference between placebo and active treatment was largely driven by subjects with low baseline scores (G.M.H., data not shown, 2014). Similar results were observed with TC5619[12] and RG3487.[11] Indeed, the effect on negative symptoms of TC5619 was not reproduced in a follow-up study with negative symptoms as a primary endpoint.[15] While not ruling out the legitimacy of these data, we do not believe they are robust enough to warrant further investigations.

The safety of ABT-126 in this study was consistent with data from our previous studies. The higher dose of 75 mg did not generate new safety signals, and there was no evidence of QTc prolongation. Constipation has been reported with RG3487 in a dose-related manner.[11] The rate of constipation was notably higher with ABT-126 75 mg compared with placebo and the lower dose, but these events were generally regarded as mild and did not result in treatment discontinuations.

There are a few design limitations worth mentioning. First, dose selection was not guided by receptor occupancy or any type of biomarkers. The doses used in this study were predicted to result in concentrations that exceeded effective preclinical concentrations. The optimal receptor occupancy rate and the presence of an inverted U-shaped dose-response curve are currently unknown. Furthermore, differences in receptor occupancy between smokers and nonsmokers, and the entire concept of receptor desensitization in smokers, are not completely understood. Second, the study was conducted in the United States only; therefore, results may not apply to other regions of the world where smoking habits and the level of care for schizophrenia may vary. Last, although steps were taken to ensure medication compliance, there were no objective measures of compliance performed in this population that is known for poor compliance. In our estimation, these limitations do not impact the interpretation of the results.

In conclusion, the α_7 agonist ABT-126 did not demonstrate a procognitive effect in subjects with schizophrenia who smoke, confirming results of a previous study. A mild effect on negative symptoms was observed.

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Potential conflicts of interest: **Drs Haig**, **Wang**, **Zhao**, **Othman**, and **Bain** are employees of AbbVie, Inc, and hold AbbVie, Inc, stock and/or stock options. **Drs Haig**, **Wang**, **Othman**, and **Bain** are also AbbVie, Inc, patent holders.

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Supplementary Material

Article Title: Efficacy and Safety of the α7 Nicotinic Acetylcholine Receptor Agonist ABT-126 in the Treatment of Cognitive Impairment Associated With Schizophrenia:

Results From a Phase 2b Randomized Controlled Study in Smokers

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List of Supplementary Material for the article

1. eTable 1 MCCB Neurocognitive Composite Score Repeated-measures Analysis (ITT)
2. eTable 2 Other Secondary Measures, Analysis of Covariance (ITT Population)
3. eTable 3 Summary of Adverse Events

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Supplementary eTable 1. MCCB Neurocognitive Composite Score Repeated-measures Analysis (ITT)

	N	Mean (SD)	LS Mean (SE) of Change	Difference from Placebo		
				LS Mean (SE)	90% CI	*P* value[a]
Baseline						
Placebo	44	32.57 (10.33)	—	—	—	—
ABT-126 25 mg	49	28.55 (12.32)	—	—	—	—
ABT-126 75 mg	46	26.02 (10.81)	—	—	—	—
Change to week 6						
Placebo	43	0.65 (5.28)	0.88 (0.80)	—	—	—
ABT-126 25 mg	48	0.54 (4.91)	0.60 (0.74)	−0.28 (1.07)	−2.06, 1.50	0.602
ABT-126 75 mg	46	0.74 (4.96)	0.78 (0.76)	−0.10 (1.10)	−1.93, 1.73	0.537
Change to week 12						
Placebo	39	1.36 (5.72)	1.42 (0.88)	—	—	—
ABT-126 25 mg	45	0.38 (5.44)	0.28 (0.81)	−1.14 (1.19)	−3.11, 0.83	0.830
ABT-126 75 mg	41	0.56 (4.63)	0.41 (0.85)	−1.01 (1.22)	−3.04, 1.01	0.796

[a]One-sided *P* value.

Abbreviations: CI = confidence interval, ITT = intent to treat, LS = least squares, MCCB = MATRICS Consensus Cognitive Battery, SD = standard deviation, SE = standard error.

Supplementary eTable 2. Other Secondary Measures, Analysis of Covariance (ITT Population)

Assessment	Placebo	ABT-126 25 mg	ABT-126 75 mg
Cigarettes/day in past week	**N = 47**	**N = 51**	**N = 46**
Baseline mean (SD)	14.26 (8.94)	16.05 (10.57)	14.26 (6.93)
LS mean change to final (SE), *P*	1.62 (1.38)	0.90 (1.28), *0.666*	0.38 (1.39), *0.763*
MTCQ-SF	**N = 45**	**N = 51**	**N = 46**
Baseline mean (SD)	45.00 (9.97)	47.31 (11.37)	46.46 (11.41)
LS mean change to final (SE), *P*	1.31 (1.69)	−0.24 (1.54), *0.775*	−1.45 (1.67), *0.905*
No. days drinking in past week[a]	**N = 14**	**N = 12**	**N = 18**
Baseline mean (SD)	0.29 (0.61)	0.58 (1.00)	0.56 (0.86)
LS mean change to final (SE), *P*	0.51 (0.37)	−0.03 (0.36), *0.827*	0.22 (0.38), *0.724*
Average No. drinks/day in past week[a]	**N = 14**	**N = 12**	**N = 18**
Baseline mean (SD)	0.29 (0.61)	0.67 (1.07)	0.47 (0.70)
LS mean change to final (SE), *P*	0.62 (0.35)	0.35 (0.34), *0.696*	0.71 (0.36), *0.422*

Note: *P* values (italicized) are one-sided specified a priori.

[a]Current drinkers in the ITT.

Abbreviations: ITT = intent to treat, LS = least squares, MTCQ-SF = Modified Tobacco Craving Questionnaire–Short Form, SD = standard deviation, SE = standard error.

Supplementary eTable 3. Summary of Adverse Events

	Placebo N=50	ABT-126 25 mg N=52	ABT-126 75 mg N=51
Any AE	25 (50.0)	27 (51.9)	24 (47.1)
Discontinued due to an AE	4 (8.0)	0	4 (7.8)
Severe AE	1 (2.0)	0	2 (3.9)
Serious AE	2 (4.0)	0	1 (2.0)
AEs reported by ≥3% of ABT-126–treated subjects[a] by MedDRA preferred term			
Constipation	0	2 (3.8)	4 (7.8)
Weight increased	2 (4.0)	3 (5.8)	3 (5.9)
Nasopharyngitis	4 (8.0)	2 (3.8)	2 (3.9)

Note: Values are presented as n (%).
[a]Both ABT-126 treatment groups combined.
Abbreviations: AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities.