Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Parallel-Group, Phase 2 Study of the Safety and Efficacy of ABT-126 in the Treatment of Cognitive Deficits in Schizophrenia (CDS) in Nonsmokers

Summary

EudraCT number	2012-000418-13
Trial protocol	GB
Global end of trial date	31 July 2014

Results information

Result version number	v2 (current)
This version publication date	18 May 2016
First version publication date	16 August 2015
Version creation reason	• Correction of full data set new version being created so writer can re-gain access to the published study to re-confirm that study has no errors.

Trial information

Trial identification

Sponsor protocol code	M10-855

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01655680
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Abbvie Deutschland GmbH & Co.KG
Sponsor organisation address	Abbott House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4XE
Public contact	Global Medical Information, AbbVie, 001 800-633-9110,
Scientific contact	George Haig, AbbVie, George.Haig@abbvie.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 July 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the efficacy and safety of ABT-126 in the treatment of cognitive deficits in schizophrenia (CDS).

Protection of trial subjects:

Subject and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy:

Subjects remained on their baseline antipsychotic treatment regimen during the entire study.

Evidence for comparator: -

Actual start date of recruitment	25 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Russian Federation: 208
Country: Number of subjects enrolled	United States: 211
Worldwide total number of subjects	432
EEA total number of subjects	13

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	430
From 65 to 84 years	2

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study included a screening/prospective stabilization period of ≥28 days. Subjects were randomized in 2 stages. 1st: in a 1:1:1:1 ratio across 4 treatment groups (ABT-126 25, 50, 75 mg or placebo). 2nd: additional subjects in a 1:1 ratio (placebo or ABT-126 50 mg [dose with best apparent benefit-risk profile following an interim efficacy analysis]).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Blinding implementation details:

The investigator, study site personnel, study sponsor (except any employees of the Sponsor who served on the Efficacy Data Monitoring Committee or the Safety Data Monitoring Committee), and subject remained blinded to each subject's randomized treatment throughout the course of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

3 placebo capsules taken orally once daily (QD) in the morning each day for 24 weeks

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects were instructed to take 3 capsules at approximately the same time each morning.

Arm title	ABT-126 25 mg

Arm description:

1 ABT-126 25 mg capsule and 2 placebo capsules taken orally QD in the morning each day for 24 weeks

Arm type	Experimental
Investigational medicinal product name	ABT-126
Investigational medicinal product code	ABT-126
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects were instructed to take 3 capsules at approximately the same time each morning.

Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
Subjects were instructed to take 3 capsules at approximately the same time each morning.

Arm title	ABT-126 50 mg

Arm description:
2 ABT-126 25 mg capsules and 1 placebo capsule taken orally QD in the morning each day for 24 weeks

Arm type	Experimental
Investigational medicinal product name	ABT-126
Investigational medicinal product code	ABT-126
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
Subjects were instructed to take 3 capsules at approximately the same time each morning.

Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
Subjects were instructed to take 3 capsules at approximately the same time each morning.

Arm title	ABT-126 75 mg

Arm description:
3 ABT-126 25 mg capsules taken orally QD in the morning each day for 24 weeks

Arm type	Experimental
Investigational medicinal product name	ABT-126
Investigational medicinal product code	ABT-126
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
Subjects were instructed to take 3 capsules at approximately the same time each morning.

Number of subjects in period 1[1]	Placebo	ABT-126 25 mg	ABT-126 50 mg
Started	144	66	151
Completed	109	54	117
Not completed	35	12	34
Consent withdrawn by subject	19	6	16
Not specified	4	-	6
Adverse event	4	4	5
Lost to follow-up	5	1	4
Noncompliance	3	1	3

Number of subjects in period 1[1]	ABT-126 75 mg
Started	70
Completed	64
Not completed	6
Consent withdrawn by subject	2
Not specified	1
Adverse event	1
Lost to follow-up	1
Noncompliance	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: After being randomized, 1 subject (ABT-126 50 mg group) did not receive a dose of study drug (and was not included in the analyses of safety or efficacy).

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
3 placebo capsules taken orally once daily (QD) in the morning each day for 24 weeks	
Reporting group title	ABT-126 25 mg
Reporting group description:	
1 ABT-126 25 mg capsule and 2 placebo capsules taken orally QD in the morning each day for 24 weeks	
Reporting group title	ABT-126 50 mg
Reporting group description:	
2 ABT-126 25 mg capsules and 1 placebo capsule taken orally QD in the morning each day for 24 weeks	
Reporting group title	ABT-126 75 mg
Reporting group description:	
3 ABT-126 25 mg capsules taken orally QD in the morning each day for 24 weeks	

Reporting group values	Placebo	ABT-126 25 mg	ABT-126 50 mg
Number of subjects	144	66	151
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	42.4	40.7	40.1
standard deviation	± 11.4	± 9.92	± 12.08
Gender categorical Units: Subjects			
Female	63	36	72
Male	81	30	79
Race Units: Subjects			
White	101	42	103
Black	40	22	45
Asian	3	1	3
Hawaiian native	0	1	0
Multi-race	0	0	0

Reporting group values	ABT-126 75 mg	Total	
Number of subjects	70	431	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	40.8		
standard deviation	± 11.22	-	

Gender categorical Units: Subjects			
Female	36	207	
Male	34	224	
Race Units: Subjects			
White	50	296	
Black	17	124	
Asian	2	9	
Hawaiian native	0	1	
Multi-race	1	1	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
3 placebo capsules taken orally once daily (QD) in the morning each day for 24 weeks	
Reporting group title	ABT-126 25 mg
Reporting group description:	
1 ABT-126 25 mg capsule and 2 placebo capsules taken orally QD in the morning each day for 24 weeks	
Reporting group title	ABT-126 50 mg
Reporting group description:	
2 ABT-126 25 mg capsules and 1 placebo capsule taken orally QD in the morning each day for 24 weeks	
Reporting group title	ABT-126 75 mg
Reporting group description:	
3 ABT-126 25 mg capsules taken orally QD in the morning each day for 24 weeks	
Subject analysis set title	ITT Cohort 1: Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects randomized in stage 1 or stage 2 to placebo, who received a dose of study drug and had verifiable study site data.	
Subject analysis set title	ITT Cohort 1: ABT-126 50 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects randomized in stage 1 or stage 2 to ABT-126 50 mg QD, who received a dose of study drug and had verifiable study site data. (ABT-126 50 mg is the dose selected at the end of stage 1 as having the best apparent benefit-risk profile for stage 2 randomization.)	

Subject analysis set title	ITT Cohort 2: Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects randomized to placebo QD in stage 1 only, who received a dose of study drug and had verifiable study site data.	
Subject analysis set title	ITT Cohort 2: ABT-126 25 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects randomized to ABT-126 25 mg QD in stage 1 only, who received a dose of study drug and had verifiable study site data.	
Subject analysis set title	ITT Cohort 2: ABT-126 50 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects randomized to ABT-126 50 mg QD in stage 1 only, who received a dose of study drug and had verifiable study site data.	
Subject analysis set title	ITT Cohort 2: ABT-126 75 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects randomized to ABT-126 75 mg QD in stage 1 only, who received a dose of study drug and had verifiable study site data.	

Primary: Change from Baseline in Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) Neurocognitive Composite Score at Week 12: ITT Cohort 1

End point title	Change from Baseline in Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) Neurocognitive Composite Score at

	Week 12: ITT Cohort 1

End point description:

The MCCB neurocognitive composite and domain scores are age- and gender-adjusted T-scores normed to have a mean score of 50 and a standard deviation of 10 in a healthy population. A higher score on the MCCB neurocognitive composite and domains represents better cognitive performance; an increasing score represents improvement. ITT Cohort 1 includes subjects from stage 1 or stage 2 who were randomized to placebo or ABT-126 50 mg.

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	ITT Cohort 1: Placebo	ITT Cohort 1: ABT-126 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116[1]	121[2]		
Units: units on a scale				
least squares mean (standard error)	2.46 (± 0.56)	2.66 (± 0.54)		

Notes:

[1] - subjects in ITT Cohort 1 with evaluable data

[2] - subjects in ITT Cohort 1 with evaluable data

Statistical analyses

Statistical analysis title	Difference between ABT-126 50 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 1: ABT-126 50 mg v ITT Cohort 1: Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.398
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	0.19
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.04
upper limit	1.43
Variability estimate	Standard error of the mean
Dispersion value	0.75

Primary: Change from Baseline in MCCB Neurocognitive Composite Score at Week 12: ITT Cohort 2

End point title	Change from Baseline in MCCB Neurocognitive Composite Score at Week 12: ITT Cohort 2

End point description:

The MCCB neurocognitive composite and domain scores are age- and gender-adjusted T-scores normed to have a mean score of 50 and a standard deviation of 10 in a healthy population.A higher score on the MCCB neurocognitive composite and domains represents better cognitive performance; an increasing score represents improvement. ITT Cohort 2 includes subjects randomized in stage 1 only, with evaluable data.

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	ITT Cohort 2: Placebo	ITT Cohort 2: ABT-126 25 mg	ITT Cohort 2: ABT-126 50 mg	ITT Cohort 2: ABT-126 75 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	56[3]	57[4]	54[5]	65[6]
Units: units on a scale				
least squares mean (standard error)	2.98 (± 0.69)	2.99 (± 0.68)	3.02 (± 0.7)	2.79 (± 0.64)

Notes:

[3] - subjects in ITT Cohort 2 with evaluable data

[4] - subjects in ITT Cohort 2 with evaluable data

[5] - subjects in ITT Cohort 2 with evaluable data

[6] - subjects in ITT Cohort 2 with evaluable data

Statistical analyses

Statistical analysis title	Difference between ABT-126 25 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 2: Placebo v ITT Cohort 2: ABT-126 25 mg
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.495
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	0.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.57
upper limit	1.6
Variability estimate	Standard error of the mean
Dispersion value	0.96

Statistical analysis title	Difference between ABT-126 50 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 2: Placebo v ITT Cohort 2: ABT-126 50 mg
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.485
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	0.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.57
upper limit	1.64
Variability estimate	Standard error of the mean
Dispersion value	0.97

Statistical analysis title	Difference between ABT-126 75 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 2: Placebo v ITT Cohort 2: ABT-126 75 mg
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	-0.19
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.72
upper limit	1.35
Variability estimate	Standard error of the mean
Dispersion value	0.93

Secondary: Change from Baseline in MCCB Composite Score at Week 24: ITT Cohort 1

End point title	Change from Baseline in MCCB Composite Score at Week 24: ITT Cohort 1

End point description:

The MCCB composite and domain scores are age- and gender-adjusted T-scores with a population mean of 50 and standard deviation of 10 in a healthy population. A higher score on the MCCB neurocognitive composite and domains represents better cognitive performance; an increasing score represents

improvement. ITT Cohort 1 includes subjects from stage 1 or stage 2 who were randomized to placebo or ABT-126 50 mg.

End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	ITT Cohort 1: Placebo	ITT Cohort 1: ABT-126 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103[7]	112[8]		
Units: units on a scale				
least squares mean (standard error)	4.37 (± 0.65)	4.41 (± 0.61)		

Notes:

[7] - subjects in ITT Cohort 1 with evaluable data

[8] - subjects in ITT Cohort 1 with evaluable data

Statistical analyses

Statistical analysis title	Difference between ABT-126 50 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 1: Placebo v ITT Cohort 1: ABT-126 50 mg
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	0.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.38
upper limit	1.47
Variability estimate	Standard error of the mean
Dispersion value	0.86

Secondary: Change from Baseline in MCCB Speed of Processing Domain Scores at Week 24: ITT Cohort 1

End point title	Change from Baseline in MCCB Speed of Processing Domain Scores at Week 24: ITT Cohort 1

End point description:

The MCCB composite and domain scores are age- and gender-adjusted T-scores with a population mean of 50 and standard deviation of 10 in a healthy population. A higher score on the MCCB neurocognitive composite and domains represents better cognitive performance; an increasing score represents improvement. ITT Cohort 1 includes subjects from stage 1 or stage 2 who were randomized to placebo

or ABT-126 50 mg.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ITT Cohort 1: Placebo	ITT Cohort 1: ABT-126 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103[9]	112[10]		
Units: units on a scale				
least squares mean (standard error)	5.49 (± 0.75)	5.2 (± 0.71)		

Notes:

[9] - subjects in ITT Cohort 1 with evaluable data

[10] - subjects in ITT Cohort 1 with evaluable data

Statistical analyses

Statistical analysis title	Difference between ABT-126 50 mg and Placebo

Statistical analysis description:

One-sided P value froma mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 1: Placebo v ITT Cohort 1: ABT-126 50 mg
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.614
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	-0.29
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.94
upper limit	1.36
Variability estimate	Standard error of the mean
Dispersion value	1

Secondary: Change from Baseline in MCCB Verbal Learning Domain Scores at Week 24: ITT Cohort 1

End point title	Change from Baseline in MCCB Verbal Learning Domain Scores at Week 24: ITT Cohort 1

End point description:

The MCCB composite and domain scores are age- and gender-adjusted T-scores with a population mean of 50 and standard deviation of 10 in a healthy population.A higher score on the MCCB neurocognitive composite and domains represents better cognitive performance; an increasing score represents improvement. ITT Cohort 1 includes subjects from stage 1 or stage 2 who were randomized to placebo or ABT-126 50 mg.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ITT Cohort 1: Placebo	ITT Cohort 1: ABT-126 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103[11]	112[12]		
Units: units on a scale				
least squares mean (standard error)	1.84 (± 0.71)	1.82 (± 0.68)		

Notes:

[11] - subjects in ITT Cohort 1 with evaluable data

[12] - subjects in ITT Cohort 1 with evaluable data

Statistical analyses

Statistical analysis title	Difference between ABT-126 50 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 1: ABT-126 50 mg v ITT Cohort 1: Placebo
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.508
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	-0.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.6
upper limit	1.57
Variability estimate	Standard error of the mean
Dispersion value	0.96

Secondary: Change from Baseline in MCCB Reasoning/Problem Solving Domain Scores at Week 24: ITT Cohort 1

End point title	Change from Baseline in MCCB Reasoning/Problem Solving Domain Scores at Week 24: ITT Cohort 1

End point description:

The MCCB composite and domain scores are age- and gender-adjusted T-scores with a population mean of 50 and standard deviation of 10 in a healthy population.A higher score on the MCCB neurocognitive composite and domains represents better cognitive performance; an increasing score represents improvement. ITT Cohort 1 includes subjects from stage 1 or stage 2 who were randomized to placebo or ABT-126 50 mg.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ITT Cohort 1: Placebo	ITT Cohort 1: ABT-126 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	99[13]	111[14]		
Units: units on a scale				
least squares mean (standard error)	3.27 (± 0.67)	3.92 (± 0.63)		

Notes:

[13] - subjects in ITT Cohort 1 with evaluable data

[14] - subjects in ITT Cohort 1 with evaluable data

Statistical analyses

Statistical analysis title	Difference between ABT-126 50 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 1: Placebo v ITT Cohort 1: ABT-126 50 mg
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.231
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	0.66
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.82
upper limit	2.13
Variability estimate	Standard error of the mean
Dispersion value	0.89

Secondary: Change from Baseline in MCCB Visual Learning Domain Scores at Week 24: ITT Cohort 1

End point title	Change from Baseline in MCCB Visual Learning Domain Scores at Week 24: ITT Cohort 1

End point description:

The MCCB composite and domain scores are age- and gender-adjusted T-scores with a population mean of 50 and standard deviation of 10 in a healthy population. A higher score on the MCCB neurocognitive composite and domains represents better cognitive performance; an increasing score represents improvement. ITT Cohort 1 includes subjects from stage 1 or stage 2 who were randomized to placebo or ABT-126 50 mg.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ITT Cohort 1: Placebo	ITT Cohort 1: ABT-126 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	102[15]	112[16]		
Units: units on a scale				
least squares mean (standard error)	3.49 (± 0.85)	2.49 (± 0.8)		

Notes:

[15] - subjects in ITT Cohort 1 with evaluable data

[16] - subjects in ITT Cohort 1 with evaluable data

Statistical analyses

Statistical analysis title	Difference between ABT-126 50 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 1: ABT-126 50 mg v ITT Cohort 1: Placebo
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.811
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	-1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.88
upper limit	0.87
Variability estimate	Standard error of the mean
Dispersion value	1.13

Secondary: Change from Baseline in MCCB Attention/Vigilance Domain Scores at Week 24: ITT Cohort 1

End point title	Change from Baseline in MCCB Attention/Vigilance Domain Scores at Week 24: ITT Cohort 1

End point description:

The MCCB composite and domain scores are age- and gender-adjusted T-scores with a population mean of 50 and standard deviation of 10 in a healthy population.A higher score on the MCCB neurocognitive composite and domains represents better cognitive performance; an increasing score represents improvement. ITT Cohort 1 includes subjects from stage 1 or stage 2 who were randomized to placebo or ABT-126 50 mg.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ITT Cohort 1: Placebo	ITT Cohort 1: ABT-126 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	100[17]	109[18]		
Units: units on a scale				
least squares mean (standard error)	3.36 (± 0.89)	2.93 (± 0.84)		

Notes:

[17] - subjects in ITT Cohort 1 with evaluable data

[18] - subjects in ITT Cohort 1 with evaluable data

Statistical analyses

Statistical analysis title	Difference between ABT-126 50 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 1: Placebo v ITT Cohort 1: ABT-126 50 mg
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.641
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	-0.43
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.42
upper limit	1.55
Variability estimate	Standard error of the mean
Dispersion value	1.2

Secondary: Change from Baseline in MCCB Social Cognition Domain Scores at Week 24: ITT Cohort 1

End point title	Change from Baseline in MCCB Social Cognition Domain Scores at Week 24: ITT Cohort 1

End point description:

The MCCB composite and domain scores are age- and gender-adjusted T-scores with a population mean of 50 and standard deviation of 10 in a healthy population. A higher score on the MCCB neurocognitive composite and domains represents better cognitive performance; an increasing score represents improvement. ITT Cohort 1 includes subjects from stage 1 or stage 2 who were randomized to placebo or ABT-126 50 mg.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ITT Cohort 1: Placebo	ITT Cohort 1: ABT-126 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	102[19]	112[20]		
Units: units on a scale				
least squares mean (standard error)	0.71 (± 0.83)	0.42 (± 0.78)		

Notes:

[19] - subjects in ITT Cohort 1 with evaluable data

[20] - subjects in ITT Cohort 1 with evaluable data

Statistical analyses

Statistical analysis title	Difference between ABT-126 50 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 1: Placebo v ITT Cohort 1: ABT-126 50 mg
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.604
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	-0.29
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.1
upper limit	1.52
Variability estimate	Standard error of the mean
Dispersion value	1.09

Secondary: Change from Baseline in University of California San Diego Performance-based Skills Assessment-2 (UPSA-2ER) at Week 24: ITT Cohort 1

End point title	Change from Baseline in University of California San Diego Performance-based Skills Assessment-2 (UPSA-2ER) at Week 24: ITT Cohort 1

End point description:

The UPSA-2ER total score range is from 0 to 120. The UPSA-2ER total score without medication management subscale range is from 0 to 100. An increasing UPSA-2ER total score represents improvement from baseline. ITT Cohort 1 includes subjects from stage 1 or stage 2 who were randomized to placebo or ABT-126 50 mg.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ITT Cohort 1: Placebo	ITT Cohort 1: ABT-126 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	102[21]	113[22]		
Units: units on s scale				
least squares mean (standard error)	5.02 (± 0.79)	6.22 (± 0.75)		

Notes:

[21] - subjects in ITT Cohort 1 with evaluable data

[22] - subjects in ITT Cohort 1 with evaluable data

Statistical analyses

Statistical analysis title	Difference between ABT-126 50 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 1: Placebo v ITT Cohort 1: ABT-126 50 mg
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.127
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	1.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.53
upper limit	2.93
Variability estimate	Standard error of the mean
Dispersion value	1.05

Secondary: Change from Baseline in UPSA-2ER at Week 24: ITT Cohort 2

End point title	Change from Baseline in UPSA-2ER at Week 24: ITT Cohort 2

End point description:

The UPSA-2ER total score range is from 0 to 120. The UPSA-2ER total score without medication management subscale range is from 0 to 100. An increasing UPSA-2ER total score represents improvement from baseline. ITT Cohort 2 includes subjects randomized in stage 1 only, with evaluable data.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ITT Cohort 2: Placebo	ITT Cohort 2: ABT-126 25 mg	ITT Cohort 2: ABT-126 50 mg	ITT Cohort 2: ABT-126 75 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47[23]	54[24]	53[25]	64[26]
Units: units on a scale				
least squares mean (standard error)	5.29 (± 1.17)	5.87 (± 1.11)	4.43 (± 1.13)	6.4 (± 1.02)

Notes:

[23] - subjects in ITT Cohort 2 with evaluable data

[24] - subjects in ITT Cohort 2 with evaluable data

[25] - subjects in ITT Cohort 2 with evaluable data

[26] - subjects in ITT Cohort 2 with evaluable data

Statistical analyses

Statistical analysis title	Difference between ABT-126 25 mg and Placebo

Statistical analysis description:

One-sided P value froma mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 2: Placebo v ITT Cohort 2: ABT-126 25 mg
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.359
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	0.58
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.07
upper limit	3.22
Variability estimate	Standard error of the mean
Dispersion value	1.6

Statistical analysis title	Difference between ABT-126 50 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 2: Placebo v ITT Cohort 2: ABT-126 50 mg

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.703
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	-0.86
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.54
upper limit	1.81
Variability estimate	Standard error of the mean
Dispersion value	1.62

Statistical analysis title	Difference between ABT-126 75 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 2: Placebo v ITT Cohort 2: ABT-126 50 mg
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.236
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	1.11
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.44
upper limit	3.66
Variability estimate	Standard error of the mean
Dispersion value	1.54

Secondary: Change from Baseline in Schizophrenia Cognition Rating Scale (SCoRS) Total Score at Week 22: ITT Cohort 1

End point title	Change from Baseline in Schizophrenia Cognition Rating Scale (SCoRS) Total Score at Week 22: ITT Cohort 1

End point description:

The SCoRS total score ranges from 4 to 80 and the SCoRS Global Rating Score ranges from 1 to 10. Decreases in the SCoRS total score and global rating scale represent improvement from baseline. ITT Cohort 1 includes subjects from stage 1 or stage 2 who were randomized to placebo or ABT-126 50 mg.

End point type	Secondary

End point timeframe:

Baseline, Week 22

End point values	ITT Cohort 1: Placebo	ITT Cohort 1: ABT-126 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97[27]	108[28]		
Units: units on a scale				
least squares mean (standard error)	-3.01 (± 0.61)	-5.19 (± 0.57)		

Notes:

[27] - subjects in ITT Cohort 1 with evaluable data

[28] - subjects in ITT Cohort 1 with evaluable data

Statistical analyses

Statistical analysis title	Difference between ABT-126 50 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 1: Placebo v ITT Cohort 1: ABT-126 50 mg
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [29]
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	-2.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.52
upper limit	-0.84
Variability estimate	Standard error of the mean
Dispersion value	0.81

Notes:

[29] - Statistically significant at the P = 0.01 level.

Secondary: Change from Baseline in SCoRS Global Rating Score at Week 22: ITT Cohort 1

End point title	Change from Baseline in SCoRS Global Rating Score at Week 22: ITT Cohort 1

End point description:

One-sided P value from repeated measures model with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured. ITT Cohort 1 includes subjects from stage 1 or stage 2 who were randomized to placebo or ABT-126 50 mg.

End point type	Secondary

End point timeframe:

Baseline, Week 22

End point values	ITT Cohort 1: Placebo	ITT Cohort 1: ABT-126 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	105[30]	112[31]		
Units: units on a scale				
least squares mean (standard error)	-0.73 (± 0.1)	-0.94 (± 0.09)		

Notes:

[30] - subjects in ITT Cohort 1 with evaluable data

[31] - subjects in ITT Cohort 1 with evaluable data

Statistical analyses

Statistical analysis title	Difference between ABT-126 50 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 1: Placebo v ITT Cohort 1: ABT-126 50 mg
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054 [32]
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	-0.21
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.42
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.13

Notes:

[32] - Trend for statistical significance at the P = 0.10 level.

Secondary: Change from Baseline in Negative Symptom Assessment Scale 16-item Version (NSA-16) at Week 24: ITT Cohort 1

End point title	Change from Baseline in Negative Symptom Assessment Scale 16-item Version (NSA-16) at Week 24: ITT Cohort 1

End point description:

The NSA-16 Total Score ranges from 16 to 96; decrease in the NSA-16 Total Score represents improvement from baseline. ITT Cohort 1 includes subjects from stage 1 or stage 2 who were randomized to placebo or ABT-126 50 mg.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ITT Cohort 1: Placebo	ITT Cohort 1: ABT-126 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	102[33]	107[34]		
Units: units on a scale				
least squares mean (standard error)	-3 (± 0.6)	-4.27 (± 0.58)		

Notes:

[33] - subjects in ITT Cohort 1 with evaluable data

[34] - subjects in ITT Cohort 1 with evaluable data

Statistical analyses

Statistical analysis title	Difference between ABT-126 50 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 1: Placebo v ITT Cohort 1: ABT-126 50 mg
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059 [35]
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	-1.27
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.61
upper limit	0.07
Variability estimate	Standard error of the mean
Dispersion value	0.81

Notes:

[35] - Trend for statistical significance at the P = 0.10 level.

Secondary: Change from Baseline in NSA-16 at Week 24: ITT Cohort 2

End point title	Change from Baseline in NSA-16 at Week 24: ITT Cohort 2

End point description:

The NSA-16 Total Score ranges from 16 to 96; decrease in the NSA-16 Total Score represents improvement from baseline. ITT Cohort 2 includes subjects randomized in stage 1 only, with evaluable data.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ITT Cohort 2: Placebo	ITT Cohort 2: ABT-126 25 mg	ITT Cohort 2: ABT-126 50 mg	ITT Cohort 2: ABT-126 75 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	49[36]	53[37]	50[38]	62[39]
Units: units on a scale				
least squares mean (standard error)	-2.56 (± 0.87)	-3.92 (± 0.86)	-4.52 (± 0.87)	-4.23 (± 0.8)

Notes:

[36] - subjects in ITT Cohort 2 with evaluable data

[37] - subjects in ITT Cohort 2 with evaluable data

[38] - subjects in ITT Cohort 2 with evaluable data

[39] - subjects in ITT Cohort 2 with evaluable data

Statistical analyses

Statistical analysis title	Difference between ABT-126 25 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 2: Placebo v ITT Cohort 2: ABT-126 25 mg
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.132
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	-1.36
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.36
upper limit	0.65
Variability estimate	Standard error of the mean
Dispersion value	1.21

Statistical analysis title	Difference between ABT-126 50 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 2: Placebo v ITT Cohort 2: ABT-126 50 mg
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.056 [40]
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	-1.96

Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.99
upper limit	0.07
Variability estimate	Standard error of the mean
Dispersion value	1.23

Notes:

[40] - Trend for statistical significance at the P = 0.10 level.

Statistical analysis title	Difference between ABT-126 75 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 2: Placebo v ITT Cohort 2: ABT-126 75 mg
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.078 [41]
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	-1.67
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.61
upper limit	0.27
Variability estimate	Standard error of the mean
Dispersion value	1.17

Notes:

[41] - Trend for statistical significance at the P = 0.10 level.

Secondary: Change from Baseline in MCCB Working Memory Domain Scores at Week 24: ITT Cohort 1

End point title	Change from Baseline in MCCB Working Memory Domain Scores at Week 24: ITT Cohort 1

End point description:

The MCCB composite and domain scores are age- and gender-adjusted T-scores with a population mean of 50 and standard deviation of 10 in a healthy population. A higher score on the MCCB neurocognitive composite and domains represents better cognitive performance; an increasing score represents improvement. ITT Cohort 1 includes subjects from stage 1 or stage 2 who were randomized to placebo or ABT-126 50 mg.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ITT Cohort 1: Placebo	ITT Cohort 1: ABT-126 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103[42]	112[43]		
Units: units on a scale				
least squares mean (standard error)	2.33 (± 0.73)	2.77 (± 0.7)		

Notes:

[42] - subjects in ITT Cohort 1 with evaluable data

[43] - subjects in ITT Cohort 1 with evaluable data

Statistical analyses

Statistical analysis title	Difference between ABT-126 50 mg and Placebo

Statistical analysis description:

One-sided P value from a mixed model for repeated measures with treatment, site, visit, baseline score, interactions of treatment and visit, and interaction of baseline score and visit; covariance structure is unstructured.

Comparison groups	ITT Cohort 1: Placebo v ITT Cohort 1: ABT-126 50 mg
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.324
Method	a mixed model for repeated measures
Parameter estimate	difference of the least square means
Point estimate	0.45
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.17
upper limit	2.06
Variability estimate	Standard error of the mean
Dispersion value	0.98

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs: From the time of study drug administration (Day 1) until 30 days following discontinuation of study drug administration (up to 24 weeks plus 30 days). SAEs collected from the time informed consent was obtained.

Adverse event reporting additional description:

All adverse events presented were treatment-emergent, defined as those that began on or after the first dose of study drug and within 6 days after the last dose of study drug. Post treatment adverse events were defined as those with onset more than 6 days after the last dose of study drug and within 30 days of the last dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

3 placebo capsules taken orally QD in the morning each day for 24 weeks

Reporting group title	ABT-126 25 mg

Reporting group description:

1 ABT-126 25 mg capsule and 2 placebo capsules taken orally QD in the morning each day for 24 weeks

Reporting group title	ABT-126 50 mg

Reporting group description:

2 ABT-126 25 mg capsules and 1 placebo capsule taken orally QD in the morning each day for 24 weeks

Reporting group title	ABT-126 75 mg

Reporting group description:

3 ABT-126 25 mg capsules taken orally QD in the morning each day for 24 weeks

Serious adverse events	Placebo	ABT-126 25 mg	ABT-126 50 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 144 (2.78%)	1 / 66 (1.52%)	4 / 151 (2.65%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 144 (0.00%)	0 / 66 (0.00%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Hiatus hernia			

subjects affected / exposed	1 / 144 (0.69%)	0 / 66 (0.00%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	1 / 144 (0.69%)	0 / 66 (0.00%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	1 / 144 (0.69%)	0 / 66 (0.00%)	2 / 151 (1.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	0 / 144 (0.00%)	1 / 66 (1.52%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 144 (0.00%)	0 / 66 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 144 (0.69%)	0 / 66 (0.00%)	0 / 151 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 144 (0.00%)	0 / 66 (0.00%)	1 / 151 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	ABT-126 75 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 70 (4.29%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Hiatus hernia			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Schizophrenia			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	ABT-126 25 mg	ABT-126 50 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 144 (15.97%)	14 / 66 (21.21%)	32 / 151 (21.19%)
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 144 (8.33%)	2 / 66 (3.03%)	16 / 151 (10.60%)
occurrences (all)	12	2	22
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 144 (1.39%)	2 / 66 (3.03%)	8 / 151 (5.30%)
occurrences (all)	2	2	8
Diarrhoea			
subjects affected / exposed	5 / 144 (3.47%)	4 / 66 (6.06%)	6 / 151 (3.97%)
occurrences (all)	5	6	6
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 144 (1.39%)	4 / 66 (6.06%)	4 / 151 (2.65%)
occurrences (all)	2	6	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 144 (2.78%)	6 / 66 (9.09%)	6 / 151 (3.97%)
occurrences (all)	4	7	6

Non-serious adverse events	ABT-126 75 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 70 (24.29%)		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 70 (7.14%)		
occurrences (all)	5		
Gastrointestinal disorders			

Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	2 / 70 (2.86%) 2 3 / 70 (4.29%) 5		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	5 / 70 (7.14%) 5		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 70 (4.29%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 July 2012	Amendment 1 was written primarily to: increase the overall sample size from 350 to 430 subjects, including an increase to 70 subjects/group in stage 1 of enrollment and an increase to 75 subjects/group in stage 2 of enrollment; delete randomization lock to review eligibility from the study design; revise stability inclusion criterion number 6 to allow hospitalized subjects if they were stable and hospitalized for social reasons; add an inclusion criterion for male contraception requirements; increase the maximum allowable body mass index and include a weight limit; specify a daily dose for oral haloperidol in the list of medications associated with TdP; delete administration of the Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, and Simpson-Angus Scale at Screening Visit 1; specify the level of interaction needed between social workers, case managers, or site staff and the subject to qualify as an informant; clarify the qualification of an informant for scales such as the SCoRS and Specific Levels of Functioning Scale; clarify cutoff value for a negative serum cotinine test for a subject's inclusion in the study; add that drug and alcohol screening could be performed onsite during the screening period; clarify that the informant only completed section number 4 of the Modified Client Socio-demographic and Service Receipt Inventory; delete the need to administer ABT-126 "preferably with food"; clarify expectations for and documentation of investigational product storage conditions; add the optional use of Automated Directly Observed Therapy and Directly Observed Therapy at sites in the United States that opted to take part in additional compliance measures; correct administrative errors; and, correct other errors.
11 February 2013	Amendment 2 was written primarily to: update the number of sites from approximately 50 to approximately 70 sites; delete the ability of the medical monitor to allow a subject who met QT interval corrected for heart rate using the Fridericia formula discontinuation criteria to continue in the study; add orphenadrine, procyclidine, and biperiden to the list of restricted anticholinergics and update throughout the protocol that anticholinergic use was prohibited for the 2 weeks prior to randomization; update Table 2; delete the specification that body temperature must have been taken orally; clarify the timing of electrocardiogram (ECG) in relation to timing of blood collections; specify that serum pregnancy test was performed by the central laboratory; add mean corpuscular volume and bicarbonate to Table 3; update description on how to handle and process samples collected for ABT-126 assay; update the scoring derivations for UPSA-2ER in Table 9; and make administrative changes to the protocol.

03 April 2013	Amendment 3 was written primarily to: increase the age range upper limit from 55 to 65 years; delete the exclusion of subjects based on their concomitant use of anticholinergic medications; clarify AbbVie's review of key eligibility criteria and sites' screening data entry responsibilities; delete the exclusion of subjects who had participated in a previous study with ABT-126; expand the list of allowable antipsychotics to include conventional antipsychotics; allow a subject to be randomized based on a negative urine cotinine test at Screening Visit 2 if the serum cotinine test result was not available at Day −1; update the timing of pharmacokinetic sample collection relative to the cognitive and functional assessments as well as the timing of ECG relative to blood sample collection, allowing the site to manage the most appropriate order of procedures based on the length of visit and time of day that the visit took place; add urine screening test for cotinine at Screening Visit 1; revise instructions for cognitive testing to ensure that scales were administered at approximately the same time of day throughout the subject's participation; update the plan for labeling the investigational product, stipulating that a separate set of investigational product was to be packaged for Romania with single panel clinical drug labels; clarify that serious adverse events were to be reported to AbbVie via fax only if the site did not have access to the electronic data capture (EDC) system or the EDC system was not operable; clarify rater requirements and expectations; and, make administrative changes to the protocol.
19 September 2013	Amendment 4 was written primarily to: clarify that while all medical safety screening procedures scheduled for Screening Visit 1 were to be performed within 42 days prior to the Day −1 visit, if > 42 days elapsed between Screening Visit 1 and the scheduled Day −1 visit, the timing for repeating medical safety screening procedures was flexible as long as the results were reviewed to confirm eligibility prior to randomization; allow alternative sources to confirm eligibility for subjects when there was difficulty obtaining medical records; emphasize the need to enter the subject's psychiatric and medical history, concomitant medications, and screening psychiatric symptom scale data into the EDC system prior to randomization; allow retesting and further clinical evaluation of subjects with certain screening laboratory abnormalities; modify exclusion criteria to avoid excluding subjects who had laboratory abnormalities but not a clinical diagnosis of liver disease or renal insufficiency; exclude subjects who were previously randomized in this study; allow the medical monitor to review suitability if subject completed participation in another clinical trial within the past 3 months prior to Screening Visit 1; add use of the Clinical Trial Subject database to identify and exclude subjects who had recently or were currently participating in other clinical trials; clarify allowed antipsychotics agents; indicate that dose or medication changes of allowed antipsychotic medications during treatment period were permitted and recommended that dose change should be communicated to AbbVie; clarify that use of all anticholinergics for treatment of extrapyramidal symptoms was restricted; add footnotes to Table 2 for clarity; clarify that AbbVie approval was needed for repeat of screening labs and additional lab tests not required by the protocol; clarify that AbbVie personnel could know the ABT-126 dose selected for the second stage of randomization; and, make other minor changes.
26 February 2014	Amendment 5 was written primarily to change the primary efficacy variable from the standard MCCB composite score to the MCCB neurocognitive composite score and include the standard MCCB composite score as a secondary efficacy variable.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported