



## 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          | v1             |
| This version publication date  | 20 April 2016  |
| First version publication date | 16 August 2015 |

#### 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  $\geq 28$  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     |
| <b>Arm title</b>             | 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.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | 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.

|   |               |
|---|---------------|
| <b>Arm title</b>  | ABT-126 50 mg |
| Arm description:<br>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.

|   |               |
|---|---------------|
| <b>Arm title</b>  | ABT-126 75 mg |
| Arm description:<br>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.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | 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             |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | <b>ABT-126 75 mg</b> |
|---|----------------------|
| 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                    |

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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:<br>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:<br>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:<br>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:<br>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<br>Units: Subjects |         |               |               |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 42.4<br>± 11.4 | 40.7<br>± 9.92 | 40.1<br>± 12.08 |
| Gender categorical<br>Units: Subjects                                   |                |                |                 |
| Female  | 63             | 36             | 72              |
| Male  | 81             | 30             | 79              |
| Race<br>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<br>Units: Subjects |               |       |  |

|   |                 |   |  |
|---|-----------------|---|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 40.8<br>± 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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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 |
|-----------------|---|

## 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 <sup>[1]</sup>    | 121 <sup>[2]</sup>          |  |  |
| 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: Placebo v ITT Cohort 1: ABT-126 50 mg |
| 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 <sup>[3]</sup>     | 57 <sup>[4]</sup>           | 54 <sup>[5]</sup>           | 65 <sup>[6]</sup>           |
| 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**

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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  |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Difference between ABT-126 50 mg and Placebo |
|-----------------------------------|--|

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**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  |

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**Statistical analysis title**

Difference between ABT-126 75 mg and Placebo

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**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  |

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**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 |
|-----------------|---|

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**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 <sup>[7]</sup>    | 112 <sup>[8]</sup>          |  |  |
| 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:<br>Placebo | ITT Cohort 1:<br>ABT-126 50<br>mg |  |  |
|-------------------------------------|--------------------------|-----------------------------------|--|--|
| Subject group type                  | Subject analysis set     | Subject analysis set              |  |  |
| Number of subjects analysed         | 103 <sup>[9]</sup>       | 112 <sup>[10]</sup>               |  |  |
| 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 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   | = 0.614   |
| 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:<br>Placebo | ITT Cohort 1:<br>ABT-126 50<br>mg |  |  |
|-------------------------------------|--------------------------|-----------------------------------|--|--|
| Subject group type                  | Subject analysis set     | Subject analysis set              |  |  |
| Number of subjects analysed         | 103 <sup>[11]</sup>      | 112 <sup>[12]</sup>               |  |  |
| Units: units on a scale             |                          |                                   |  |  |
| least squares mean (standard error) | 1.84 ( $\pm$ 0.71)       | 1.82 ( $\pm$ 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:<br>Placebo | ITT Cohort 1:<br>ABT-126 50<br>mg |  |  |
|-------------------------------------|--------------------------|-----------------------------------|--|--|
| Subject group type                  | Subject analysis set     | Subject analysis set              |  |  |
| Number of subjects analysed         | 99 <sup>[13]</sup>       | 111 <sup>[14]</sup>               |  |  |
| 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

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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:<br>Placebo | ITT Cohort 1:<br>ABT-126 50<br>mg |  |  |
|-------------------------------------|--------------------------|-----------------------------------|--|--|
| Subject group type                  | Subject analysis set     | Subject analysis set              |  |  |
| Number of subjects analysed         | 102 <sup>[15]</sup>      | 112 <sup>[16]</sup>               |  |  |
| 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:<br>Placebo | ITT Cohort 1:<br>ABT-126 50<br>mg |  |  |
|-------------------------------------|--------------------------|-----------------------------------|--|--|
| Subject group type                  | Subject analysis set     | Subject analysis set              |  |  |
| Number of subjects analysed         | 100 <sup>[17]</sup>      | 109 <sup>[18]</sup>               |  |  |
| Units: units on a scale             |                          |                                   |  |  |
| least squares mean (standard error) | 3.36 ( $\pm$ 0.89)       | 2.93 ( $\pm$ 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:<br>Placebo | ITT Cohort 1:<br>ABT-126 50<br>mg |  |  |
|-------------------------------------|--------------------------|-----------------------------------|--|--|
| Subject group type                  | Subject analysis set     | Subject analysis set              |  |  |
| Number of subjects analysed         | 102 <sup>[19]</sup>      | 112 <sup>[20]</sup>               |  |  |
| 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:<br>Placebo | ITT Cohort 1:<br>ABT-126 50<br>mg |  |  |
|-------------------------------------|--------------------------|-----------------------------------|--|--|
| Subject group type                  | Subject analysis set     | Subject analysis set              |  |  |
| Number of subjects analysed         | 102 <sup>[21]</sup>      | 113 <sup>[22]</sup>               |  |  |
| Units: units on s scale             |                          |                                   |  |  |
| least squares mean (standard error) | 5.02 ( $\pm$ 0.79)       | 6.22 ( $\pm$ 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 <sup>[23]</sup>    | 54 <sup>[24]</sup>          | 53 <sup>[25]</sup>          | 64 <sup>[26]</sup>          |
| Units: units on a scale             |                       |                             |                             |                             |
| least squares mean (standard error) | 5.29 ( $\pm$ 1.17)    | 5.87 ( $\pm$ 1.11)          | 4.43 ( $\pm$ 1.13)          | 6.4 ( $\pm$ 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 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   | 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                                 |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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:<br>Placebo | ITT Cohort 1:<br>ABT-126 50<br>mg |  |  |
|-------------------------------------|--------------------------|-----------------------------------|--|--|
| Subject group type                  | Subject analysis set     | Subject analysis set              |  |  |
| Number of subjects analysed         | 97 <sup>[27]</sup>       | 108 <sup>[28]</sup>               |  |  |
| Units: units on a scale             |                          |                                   |  |  |
| least squares mean (standard error) | -3.01 ( $\pm$ 0.61)      | -5.19 ( $\pm$ 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 <sup>[29]</sup>                             |
| 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:<br>Placebo | ITT Cohort 1:<br>ABT-126 50<br>mg |  |  |
|-------------------------------------|--------------------------|-----------------------------------|--|--|
| Subject group type                  | Subject analysis set     | Subject analysis set              |  |  |
| Number of subjects analysed         | 105 <sup>[30]</sup>      | 112 <sup>[31]</sup>               |  |  |
| 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 <sup>[32]</sup>                             |
| 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:<br>Placebo | ITT Cohort 1:<br>ABT-126 50<br>mg |  |  |
|-------------------------------------|--------------------------|-----------------------------------|--|--|
| Subject group type                  | Subject analysis set     | Subject analysis set              |  |  |
| Number of subjects analysed         | 102 <sup>[33]</sup>      | 107 <sup>[34]</sup>               |  |  |
| 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 <sup>[35]</sup>                             |
| 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 <sup>[36]</sup>    | 53 <sup>[37]</sup>          | 50 <sup>[38]</sup>          | 62 <sup>[39]</sup>          |
| 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 <sup>[40]</sup>                             |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[41]</sup>                             |
| 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:<br>Placebo | ITT Cohort 1:<br>ABT-126 50<br>mg |  |  |
|-------------------------------------|--------------------------|-----------------------------------|--|--|
| Subject group type                  | Subject analysis set     | Subject analysis set              |  |  |
| Number of subjects analysed         | 103 <sup>[42]</sup>      | 112 <sup>[43]</sup>               |  |  |
| 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           |
| <b>Psychiatric disorders</b>                    |                 |                |                 |
| 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           |
| <b>Infections and infestations</b>              |                 |                |                 |
| 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           |

|   |                |  |  |
|---|----------------|--|--|
| <b>Serious adverse events</b>                     | 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 %

| <b>Non-serious adverse events</b>                     | 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                 |

| <b>Non-serious adverse events</b>                     | 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<br>subjects affected / exposed<br>occurrences (all)                                   | 2 / 70 (2.86%)<br>2 |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                      | 3 / 70 (4.29%)<br>5 |  |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)              | 5 / 70 (7.14%)<br>5 |  |  |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 3 / 70 (4.29%)<br>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