



## Clinical trial results:

### Long-Term Safety and Tolerability of ABT-126 in Subjects with Mild-to-Moderate Alzheimer's Disease: An Open-Label Extension Study for Subjects Completing Study M10-985

#### Summary

EudraCT number	2011-004780-75
Trial protocol	GB
Global end of trial date	12 March 2014

#### Results information

Result version number	v1
This version publication date	20 April 2016
First version publication date	10 July 2015

#### Trial information

##### Trial identification

Sponsor protocol code	M11-427
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01676935
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	Laura Gault MD PhD, AbbVie, laura.gault@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	12 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 March 2014
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The objective of this study is to evaluate the long-term safety and tolerability of ABT-126 in subjects with mild-to-moderate Alzheimer's disease (AD) in 28-week open-label extension of study 2011-002004-32 (M10-985).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 August 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 124
Country: Number of subjects enrolled	Ukraine: 46
Country: Number of subjects enrolled	United States: 26
Country: Number of subjects enrolled	South Africa: 85
Country: Number of subjects enrolled	Poland: 27
Country: Number of subjects enrolled	United Kingdom: 41
Worldwide total number of subjects	349
EEA total number of subjects	68

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)	52
From 65 to 84 years	264
85 years and over	33

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Only subjects randomized into Study 2011-002004-32 who completed dosing through Week 24 of that study were eligible for Study 2011-004780-75. Each subject had routine safety procedures/clinical laboratory tests performed either on Day -1 or as part of the 2011-002004-32 Week 24 visit. Subjects who met the selection criteria were entered into study.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	ABT-126
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Arm description:

ABT-126 25 mg hard gelatin capsule administered orally beginning at 75 mg once daily (QD), which could have been adjusted downward in 25 mg increments with the permission of the AbbVie medical monitor for safety or tolerability issues.

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

Dosage and administration details:

The allowable total daily dose of ABT-126 was 25 mg to 75 mg.

Number of subjects in period 1	ABT-126
Started	349
Completed	183
Not completed	166
Consent withdrawn by subject	19
Study terminated prematurely	129
Not specified	3
Adverse event	13
Lost to follow-up	2

## Baseline characteristics

### Reporting groups

Reporting group title	ABT-126
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Reporting group description:

ABT-126 25 mg hard gelatin capsule administered orally beginning at 75 mg once daily (QD), which could have been adjusted downward in 25 mg increments with the permission of the AbbVie medical monitor for safety or tolerability issues.

Reporting group values	ABT-126	Total	
Number of subjects	349	349	
Age categorical			
Units: Subjects			
< 75 years	167	167	
≥ 75 years	182	182	
Age continuous			
Units: years			
arithmetic mean	74.1		
standard deviation	± 7.88	-	
Gender categorical			
Units: Subjects			
Female	210	210	
Male	139	139	

## End points

### End points reporting groups

Reporting group title	ABT-126
Reporting group description: ABT-126 25 mg hard gelatin capsule administered orally beginning at 75 mg once daily (QD), which could have been adjusted downward in 25 mg increments with the permission of the AbbVie medical monitor for safety or tolerability issues.	

### Primary: Number of Subjects With Treatment Emergent Adverse Events

End point title	Number of Subjects With Treatment Emergent Adverse
End point description: A treatment-emergent adverse event (TEAE) was defined as any adverse event that began or worsened in severity on or after the first day of ABT-126 dosing in Study M11-427 and no more than 30 days after the last study drug dose date.	
End point type	Primary
End point timeframe: Day -1 through Week 28 (or premature discontinuation) of treatment plus 30 days. Mean (SD) number of treatment exposure days was 163.1 (48.15).	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Safety data was summarized using descriptive statistics. No statistical testing was performed.

End point values	ABT-126			
Subject group type	Reporting group			
Number of subjects analysed	349			
Units: subjects				
Any adverse event (AE)	167			
AE w/reasonable possibility of relatedness to drug	66			
Any severe AE	18			
Any serious AE	17			
AE leading to discontinuation of study drug	17			
Any fatal AE	4			
All deaths	4			

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects Meeting Criteria for Potentially Clinically Significant Hematology Values

End point title	Number of Subjects Meeting Criteria for Potentially Clinically Significant Hematology Values <sup>[2]</sup>
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End point description:

F=female, M=male

End point type	Primary
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End point timeframe:

Day -1 through Week 28 (or premature discontinuation).

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Safety data was summarized using descriptive statistics. No statistical testing was performed.

End point values	ABT-126			
Subject group type	Reporting group			
Number of subjects analysed	349 <sup>[3]</sup>			
Units: subjects				
Hemoglobin < 90 g/L (F) or < 100 g/L (M); n=345	1			
Platelet count < $95 \times 10^9/L$ ; n=344	1			
White blood cell count < $2.8 \times 10^9/L$ ; n=345	15			
White blood cell count > $18 \times 10^9/L$ ; n=345	2			
Neutrophils < $1.2 \times 10^9/L$ ; n=345	13			
Lymphocytes < $0.75 \times 10^9/L$ ; n=345	19			

Notes:

[3] - n=subjects with post-baseline values for each parameter

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects Meeting Criteria for Potentially Clinically Significant Chemistry Values

End point title	Number of Subjects Meeting Criteria for Potentially Clinically Significant Chemistry Values <sup>[4]</sup>
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End point description:

ULN=upper limit of normal, F=female, M=male

End point type	Primary
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End point timeframe:

Day -1 through Week 28 (or premature discontinuation).

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Safety data was summarized using descriptive statistics. No statistical testing was performed.

End point values	ABT-126			
Subject group type	Reporting group			
Number of subjects analysed	345 <sup>[5]</sup>			
Units: subjects				
Alanine aminotransferase > 3*ULN	3			
Aspartate aminotransferase > 3*ULN	2			
Total bilirubin > 29 µmol/L	2			

Creatinine > 159 (F) or > 180 (M) $\mu$ mol/L	4			
Uric acid > 500 (F) or > 590 (M) $\mu$ mol/L	7			
Calcium < 1.75 mmol/L	5			
Sodium < 126 mmol/L	7			
Sodium > 156 mmol/L	1			
Potassium < 3 mmol/L	2			
Potassium > 6 mmol/L	3			
Glucose < 2.75 mmol/L	3			
Glucose > 16.5 mmol/L	2			

Notes:

[5] - subjects with post-baseline values for each parameter

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects Meeting Criteria for Potentially Clinically Significant Vital Sign and Weight Values

End point title	Number of Subjects Meeting Criteria for Potentially Clinically Significant Vital Sign and Weight Values <sup>[6]</sup>
End point description:	
SBP=systolic blood pressure	
End point type	Primary
End point timeframe:	
Day -1 through Week 28 (or premature discontinuation).	

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Safety data was summarized using descriptive statistics. No statistical testing was performed.

<b>End point values</b>	ABT-126			
Subject group type	Reporting group			
Number of subjects analysed	345 <sup>[7]</sup>			
Units: subjects				
SBP $\geq$ 180 mmHg; $\geq$ 40 mmHg increase	2			
Weight $\geq$ 7% decrease	25			
Weight $\geq$ 7% increase	23			
Temperature $\geq$ 1.1° C decrease	3			
Temperature > 38.5° C or $\geq$ 1.1° C increase	5			

Notes:

[7] - subjects with post-baseline values for each parameter

## Statistical analyses

No statistical analyses for this end point

### Primary: Columbia-Suicide Severity Rating Scale (C-SSRS) Summary

End point title	Columbia-Suicide Severity Rating Scale (C-SSRS) Summary <sup>[8]</sup>
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**End point description:**

The C-SSRS is a systematically administered instrument developed to track suicidal adverse events across a treatment study. The instrument is designed to assess suicidal behavior and ideation, track and assess all suicidal events, as well as the lethality of attempts. The C-SSRS was administered to the subject and an assessment completed using information gathered from the subject and caregiver. Summary data presents the number of subjects with suicidal ideation or behavior at any time during the study.

End point type	Primary
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**End point timeframe:**

Day -1 through Week 28 (or premature discontinuation) plus 30 days follow-up

**Notes:**

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Safety data was summarized using descriptive statistics. No statistical testing was performed.

End point values	ABT-126			
Subject group type	Reporting group			
Number of subjects analysed	349			
Units: subjects				
Ideation: wish to be dead	14			
Ideation: non-specific active suicidal thoughts	2			
Ideation: active thoughts without intent to act	1			
Ideation: active thoughts with some intent/no plan	0			
Ideation: active thoughts with plan and intent	0			
Behavior: actual attempt	0			
Behavior: interrupted attempt	0			
Behavior: aborted attempt	0			
Behavior: preparatory acts or behavior	0			
Behavior: suicidal behavior	1			
Behavior: completed suicide	0			
Subjects with suicidal ideations	14			
Subjects with suicidal ideations only	14			
Subjects with suicidal behaviors	1			
Subjects with suicidal behaviors or ideations	15			

**Statistical analyses**

No statistical analyses for this end point

**Primary: Mean Change from Baseline in Cornell Scale for Depression in Dementia (CSDD)**

End point title	Mean Change from Baseline in Cornell Scale for Depression in Dementia (CSDD) <sup>[9]</sup>
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**End point description:**

The CSDD is a 19-item interviewer-rated scale for assessing the signs and symptoms of major depression in patients with dementia. Information is obtained from two semi-structured interviews: an interview with the subject and an interview with the caregiver. Each item is ranked on a severity scale of 0 to 2 (0 = absent; 1 = mild or intermittent; 2 = severe). The individual item scores are summed for a

total score. The CSDD scores range from 0 to 38, with higher scores indicative of greater depression. Scores above 10 indicate a probable major depression.

End point type	Primary
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End point timeframe:

Baseline (Day -1), Final Evaluation (up to Week 28)

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Safety data was summarized using descriptive statistics. No statistical testing was performed.

<b>End point values</b>	ABT-126			
Subject group type	Reporting group			
Number of subjects analysed	220 <sup>[10]</sup>			
Units: units on a scale				
arithmetic mean (standard deviation)	0.36 (± 2.42)			

Notes:

[10] - subjects with baseline and post-baseline values

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects Meeting Criteria for Potentially Clinically Significant Electrocardiogram Values

End point title	Number of Subjects Meeting Criteria for Potentially Clinically Significant Electrocardiogram Values <sup>[11]</sup>
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End point description:

Measurements include heart rate, RR interval, PR interval, QRS duration and QT intervals.

End point type	Primary
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End point timeframe:

Day -1 through Week 28 (or premature discontinuation).

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Safety data was summarized using descriptive statistics. No statistical testing was performed.

<b>End point values</b>	ABT-126			
Subject group type	Reporting group			
Number of subjects analysed	344 <sup>[12]</sup>			
Units: subjects				
Bazett QTC interval > 500 msec	7			
Bazett QTC interval > 60 msec increase	7			
Fredericia QTC interval > 500 msec	3			

Notes:

[12] - subjects with post-baseline values for the respective parameter

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day -1 through Week 28 (or premature discontinuation) of treatment plus 30 days. Mean (SD) number of treatment exposure days was 163.1 (48.15).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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### Reporting groups

Reporting group title	ABT-126
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Reporting group description:

ABT-126 25 mg hard gelatin capsule administered orally beginning at 75 mg once daily (QD), which could have been adjusted downward in 25 mg increments with the permission of the AbbVie medical monitor for safety or tolerability issues.

Serious adverse events	ABT-126		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 349 (4.87%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
anxiety			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delusion			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	2 / 349 (0.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Aortic valve disease			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mitral valve disease			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial fibrosis			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myocardial ischaemia			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Brain stem syndrome			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cerebral infarction			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Convulsion			
subjects affected / exposed	3 / 349 (0.86%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Hearing impaired			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal necrosis			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vomiting			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Mobility decreased			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Respiratory tract infection bacterial			

subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 349 (0.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	ABT-126		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 349 (15.47%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	15 / 349 (4.30%)		
occurrences (all)	22		
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 349 (3.15%)		
occurrences (all)	12		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	17 / 349 (4.87%)		
occurrences (all)	17		
Nausea			

subjects affected / exposed occurrences (all)	7 / 349 (2.01%) 7		
Psychiatric disorders Aggression subjects affected / exposed occurrences (all)	6 / 349 (1.72%) 8		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 July 2013	<p>The purpose of this amendment was to make the following changes:</p> <ul style="list-style-type: none"><li>• Add additional contact information to Title Page, Section 6.5, and Section 7.0 for AbbVie Medical Monitor.</li><li>• Delete reference from Table 1 (Study Activities) stating study drug dispensed at Day -1 visit may be re-dispensed at Day 14 and Week 4, in order to align the Study Activities Table with text in Section 5.5.2.1 as study drug product was not to be re-dispensed.</li><li>• Add rating scales to assess apathy symptoms associated with Alzheimer's disease (AD) measured by Dementia in Apathy Interview and Rating (DAIR) and the Apathy Evaluation Scale (AES).</li><li>• Add rating scales to assess impairment of executive function associated with Alzheimer's disease measured by change in behavioral symptoms (Everyday Cognition (eCOG), Frontal Systems Behavior Scale (FrSBe), as well cognitive performance tests (such as Controlled Oral Word Association Test (COWAT), Categorical Verbal Fluency Test (CFT), Trails Making Test A (TMT-A) and Trails Making Test B (TMT-B), Digit Symbol Substitution Test (DSST), Letter Number Sequencing (LNS), Spatial Span (SS) Test, and Digit Span Backward (DSB).</li><li>• Update language in Section 5.3.1.1 (12-Lead ECG) regarding the timing of the ECGs relative to blood sample collection. Delete reference to blinded study drug assignment, in order to clarify that ECGs should be obtained prior to any blood collections, only if these procedures are scheduled within approximately 30 minutes of each other.</li><li>• Delete the 14 day follow-up visit from the text in Section 5.4.1, in order to ensure consistency within the protocol.</li><li>• Correction in Section 8.1.3.1 (Cumulative Data Set) regarding the baseline for those subjects who received ABT-126 in Study M10-985 and who had a gap of 7 days or less between studies.</li><li>• Other changes to the protocol were for administrative purposes, to correct typographical errors or ensure consistency throughout the protocol.</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This extension study was terminated on 15 January 2014 due to the insufficient efficacy of ABT-126 in the double-blind phase 2 study 2011-002004-32 (M10-985) to support further clinical development.

Notes: