



Clinical trial results:

An open-label, non-randomized study to evaluate the efficacy and safety of BAY 94-9172 (ZK 6013443) positron emission tomography (PET) imaging for detection/exclusion of cerebral β -amyloid when compared to postmortem histopathology

Summary

EudraCT number	2009-012569-79
Trial protocol	FR DE
Global end of trial date	24 December 2013

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	

Trial information

Trial identification

Sponsor protocol code	BAY94-9172/14595
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01020838
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Piramal Imaging SA
Sponsor organisation address	Route de l'Ecole 13, Matran, Switzerland, 1753
Public contact	Jürgen Hirschfeld, PhD, Piramal Imaging GmbH, +49 30461124615, juergen.hirschfeld@piramal.com
Scientific contact	Andrew Stephens, MD, PhD, Piramal Imaging GmbH, +49 30461124604, andrew.stephens@piramal.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	30 September 2014

Is this the analysis of the primary completion data?	Yes
Primary completion date	24 December 2013
Global end of trial reached?	Yes
Global end of trial date	24 December 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the sensitivity and specificity of the visual assessment of regional tracer uptake in the florbetaben (also referred to as BAY 94-9172) PET images compared to histological verification of the presence or absence of cerebral β -amyloid in the respective postmortem specimens as the standard of truth (SOT). To determine the sensitivity and specificity of the majority read "whole brain" visual assessment in detecting/excluding cerebral neuritic β -amyloid plaques compared with the corresponding histopathological SOT. To determine sensitivity and specificity of the subject level composite SUVR quantification calculated based on pathology results covering all available data. To determine the subject level composite SUVRs by SOT for baseline and available follow-up scans.

Protection of trial subjects:

The trial was conducted in accordance with GCP Guidelines, the Declaration of Helsinki and according to national law. The trial started only after regulatory and ethical approval. Recruitment only started after the protocol was signed by the investigator. Only patients with informed consent were included in the study. All necessary insurances to guarantee compensation of patients in the case of adverse reactions were in place.

In view of the positive safety profile of this investigational drug, including the minimal radiation applied by the tracer administration and transmission scanning, the foreseeable risks to the subjects and negative impact on the subject's well-being were considered low.

Background therapy:

Prior medication (or medication history) refers to medication taken within 8 weeks (recommended screening period, but up to 12 weeks is acceptable) before injection of the study drug. Concomitant medication refers to medication received by the subject from the point of injection of the study drug. Study participants received prior and concomitant medications during the study. Prior and concomitant medication was frequently used in the study and captured via the CRF. The most frequently documented concomitant medication by MedDRA preferred term included sodium chloride (32.9% of subjects), acetyl salicylic acid (28.2% of subjects), memantine (27.8% of subjects), donepezil (25.0% of subjects), paracetamol (15.7% of subjects), furosemide (13.9% of subjects), rivastigmine (12.0% of subjects), simvastatin (11.6% of subjects), and citalopram (11.1% of subjects).

Evidence for comparator:

There is no comparator group available.

Actual start date of recruitment	25 November 2009
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 States: 70
Country: Number of subjects enrolled	France: 35
Country: Number of subjects enrolled	Germany: 45
Country: Number of subjects enrolled	Japan: 54
Country: Number of subjects enrolled	Australia: 14
Worldwide total number of subjects	218
EEA total number of subjects	80

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)	42
From 65 to 84 years	123
85 years and over	53

Subject disposition

Recruitment

Recruitment details:

The main study population consisted of male or female subjects of any ethnic group with short life-expectancy (< 3 years). Both, subjects with a low probability of cerebral β -amyloid deposition and those with a high probability of β -amyloid deposition were included. Young cognitively normal HVs served as negative control.

Pre-assignment

Screening details:

A total of 253 subjects were screened at 15 study centers worldwide. Of the 253 screened subjects, 218 subjects were enrolled and assigned to treatment while 35 subjects were considered screening failures.

Pre-assignment period milestones

Number of subjects started	253 ^[1]
Intermediate milestone: Number of subjects	Safety Analysis Set: 216
Number of subjects completed	216

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Never treated: 2
Reason: Number of subjects	Screening failure: 35

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 35 subjects were screening failures and 2 subjects were never treated.

Period 1

Period 1 title	Safety Analysis Set (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Safety Analysis Set
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Florbetaben
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Study participants were administered florbetaben under the direct supervision of a nuclear physician or designee. Access into a large vein (e.g., antecubital vein) was established using a suitable indwelling catheter (e.g., Venflow). To avoid extravasation of florbetaben, correct localization of the catheter was ensured by a test injection of normal saline prior to the injection of florbetaben.

Number of subjects in period 1^[2]	Safety Analysis Set		
Started	216		
Completed	216		

Notes:

[2] - 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: Two patients were excluded from this population because injection of florbetaben was not done.

Baseline characteristics

Reporting groups

Reporting group title	Safety Analysis Set
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Reporting group description: -

Reporting group values	Safety Analysis Set	Total	
Number of subjects	216	216	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	42	42	
From 65-84 years	121	121	
85 years and over	53	53	
Age continuous			
Units: years			
arithmetic mean	74.39		
standard deviation	± 15.44	-	
Gender categorical			
Units: Subjects			
Female	104	104	
Male	112	112	

Subject analysis sets

Subject analysis set title	Primary Efficacy Analysis
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

To determine the sensitivity and specificity of the visual assessment of regional tracer uptake in the florbetaben (also referred to as BAY 94-9172) PET images compared to histological verification of the presence or absence of cerebral-amyloid in the respective postmortem specimens as the standard of truth (SoT).

Subject analysis set title	Final Analysis-Whole Brain
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

To determine the sensitivity and specificity of the composite "whole brain" (per subject) regional visual assessment collapsed from the regional PET visual assessment results in detecting/excluding cerebral β -amyloid plaques based on the "whole brain" histopathological verification of the presence/absence of β -amyloid deposition based on the corresponding histopathological standard of truth.

Subject analysis set title	First Annual Repeat Injection
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Patients returning for first follow-up administration and PET scan.

Subject analysis set title	Second Annual Repeat Injection
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients returning for second follow-up Administration and PET scan.	

Reporting group values	Primary Efficacy Analysis	Final Analysis-Whole Brain	First Annual Repeat Injection
Number of subjects	41	97	91
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	18	19
From 65-84 years	18	49	51
85 years and over	12	30	21
Age continuous Units: years			
arithmetic mean	68.51	74.65	75
standard deviation	± 24.96	± 18.94	± 11.33
Gender categorical Units: Subjects			
Female	15	40	48
Male	26	57	43

Reporting group values	Second Annual Repeat Injection		
Number of subjects	34		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	8		
From 65-84 years	19		
85 years and over	7		
Age continuous Units: years			
arithmetic mean	74.35		
standard deviation	± 11.67		
Gender categorical Units: Subjects			
Female	18		
Male	16		

End points

End points reporting groups

Reporting group title	Safety Analysis Set
Reporting group description: -	
Subject analysis set title	Primary Efficacy Analysis
Subject analysis set type	Sub-group analysis
Subject analysis set description: To determine the sensitivity and specificity of the visual assessment of regional tracer uptake in the florbetaben (also referred to as BAY 94-9172) PET images compared to histological verification of the presence or absence of cerebral-amyloid in the respective postmortem specimens as the standard of truth (SoT).	
Subject analysis set title	Final Analysis-Whole Brain
Subject analysis set type	Sub-group analysis
Subject analysis set description: To determine the sensitivity and specificity of the composite "whole brain" (per subject) regional visual assessment collapsed from the regional PET visual assessment results in detecting/excluding cerebral β -amyloid plaques based on the "whole brain" histopathological verification of the presence/absence of β -amyloid deposition based on the corresponding histopathological standard of truth.	
Subject analysis set title	First Annual Repeat Injection
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients returning for first follow-up administration and PET scan.	
Subject analysis set title	Second Annual Repeat Injection
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients returning for second follow-up Administration and PET scan.	

Primary: Sensitivity (Primary Efficacy Analysis)

End point title	Sensitivity (Primary Efficacy Analysis) ^[1]
End point description: The sensitivity/specificity of the visual assessment were calculated based on the majority read assessment of regional tracer uptake. This result was derived from assessments by 3 independent readers for brain regions of a subject where a Standard of Truth (SOT) was available. The SOT for this analysis was a centralized histopathological determination of β -amyloid presence/absence based on both Bielschowsky silver and immunohistochemical staining. Based on the PET images, a brain region was classified as "normal" or "abnormal" depending on the presence or absence of regional tracer uptake in the respective region. "Normal" therefore meant absence of β -amyloid and "abnormal" presence of β -amyloid. Sensitivity was defined as the percentage of abnormal brain regions from all regions where an SOT was available and the SOT was " β -amyloid present". Specificity was defined as the percentage of normal brain regions from all regions where an SOT was available and was " β -amyloid not present".	
End point type	Primary
End point timeframe: 90-110 minutes post injection (PET image acquisition)	

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: The statistical analysis is provided as separate attachment.

End point values	Primary Efficacy Analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	41			
Units: Sensitivity [%]				
number (not applicable)				
Total	77.36			
Frontal Cortex	85.71			
Occipital Cortex	88.89			
Hippocampus	57.14			
Anterior Cingulate Cortex	90			
Posterior Cingulate Cortex	81.82			
Cerebellar Cortex	0			

Attachments (see zip file)	Sensitivity Statistical Analysis Primary
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Statistical analyses

No statistical analyses for this end point

Primary: Specificity (Primary Efficacy Analysis)

End point title	Specificity (Primary Efficacy Analysis) ^[2]
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End point description:

The sensitivity/specificity of the visual assessment were calculated based on the majority read assessment of regional tracer uptake. This result was derived from assessments by 3 independent readers for brain regions of a subject where a Standard of Truth (SOT) was available. The SOT for this analysis was a centralized histopathological determination of β -amyloid presence/absence based on both Bielschowsky silver and immunohistochemical staining. Based on the PET images, a brain region was classified as "normal" or "abnormal" depending on the presence or absence of regional tracer uptake in the respective region. "Normal" therefore meant absence of β -amyloid and "abnormal" presence of β -amyloid. Sensitivity was defined as the percentage of abnormal brain regions from all regions where an SOT was available and the SOT was " β -amyloid present". Specificity was defined as the percentage of normal brain regions from all regions where an SOT was available and was " β -amyloid not present".

End point type	Primary
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End point timeframe:

90-110 minutes post injection (PET image acquisition)

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: The statistical analysis is provided as separate attachment.

End point values	Primary Efficacy Analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	41			
Units: Specificity [%]				
number (not applicable)				
Total	94.2			
Frontal Cortex	95			
Occipital Cortex	86.36			
Hippocampus	100			

Anterior Cingulate Cortex	85.71			
Posterior Cingulate Cortex	94.44			
Cerebellar Cortex	100			

Attachments (see zip file)	Specificity Statistical Analysis Primary
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Statistical analyses

No statistical analyses for this end point

Secondary: Sensitivity and Specificity (Whole brain, BSS)

End point title	Sensitivity and Specificity (Whole brain, BSS)
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End point description:

Sensitivity and specificity of the whole brain visual assessment were calculated. Any brain with a region classified as abnormal from PET imaging was to be classified as abnormal for the "whole brain" assessment. This result was derived from assessments by 3 independent readers for a subject where a Standard of Truth (SOT) was available. The SOT for this analysis was based on a centralized histopathological assessment of the presence/absence of β -amyloid based on Bielschowsky silver staining (SOT 1). The sensitivity was defined as the proportion of brains classified as abnormal from all brains where this SOT was available and was " β -amyloid present". The specificity was defined as the proportion of brains classified as normal from all brains where this SOT was available and was " β -amyloid not present".

End point type	Secondary
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End point timeframe:

90-110 minutes post injection (PET image acquisition)

End point values	Final Analysis-Whole Brain			
Subject group type	Subject analysis set			
Number of subjects analysed	97			
Units: [%]				
number (confidence interval 95%)				
Sensitivity	96.49 (91.71 to 100)			
Specificity	85 (73.93 to 96.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Sensitivity and Specificity (Whole brain, BSS+IHC)

End point title	Sensitivity and Specificity (Whole brain, BSS+IHC)
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End point description:

Sensitivity and specificity of the whole brain visual assessment were calculated. Any brain with a region classified as abnormal from PET imaging was to be classified as abnormal for the "whole brain" assessment. This result was derived from assessments by 3 independent readers for a subject where a

Standard of Truth (SOT) was available. The SOT for this analysis was based on a centralized histopathological assessment of the presence/absence of β -amyloid based on Bielschowsky silver staining and immunohistochemistry (SOT 2). The sensitivity was defined as the proportion of brains classified as abnormal from all brains where this SOT was available and was " β -amyloid present". The specificity was defined as the proportion of brains classified as normal from all brains where this SOT was available and was " β -amyloid not present".

End point type	Secondary
End point timeframe:	
90-110 minutes post injection (PET image acquisition)	

End point values	Final Analysis- Whole Brain			
Subject group type	Subject analysis set			
Number of subjects analysed	97			
Units: [%]				
number (confidence interval 95%)				
Sensitivity	96.72 (92.25 to 100)			
Specificity	94.44 (86.96 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Sensitivity and Specificity (Whole brain, CERAD)

End point title	Sensitivity and Specificity (Whole brain, CERAD)
End point description:	
Sensitivity and specificity of the whole brain visual assessment were calculated. Any brain with a region classified as abnormal from PET imaging was to be classified as abnormal for the "whole brain" assessment. This result was derived from assessments by 3 independent readers for a subject where a Standard of Truth (SOT) was available. The SOT for this analysis was based on a histopathological assessment of the presence/absence of β -amyloid according to CERAD Criteria (SOT 3). The sensitivity was defined as the proportion of brains classified as abnormal from all brains where this SOT was available and was " β -amyloid present". The specificity was defined as the proportion of brains classified as normal from all brains where this SOT was available and was " β -amyloid not present".	
End point type	Secondary
End point timeframe:	
90-110 minutes post injection (PET image acquisition)	

End point values	Final Analysis-Whole Brain			
Subject group type	Subject analysis set			
Number of subjects analysed	97			
Units: [%]				
number (confidence interval 95%)				
Sensitivity	96.49 (91.71 to 100)			
Specificity	85 (73.93 to 96.07)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Sensitivity of Subject Level Composite SUVR by SOT

End point title	Sensitivity of Subject Level Composite SUVR by SOT
End point description:	
Sensitivity and Specificity of subject level composite Standard Uptake Value Ratios (SUVR) by SOT for subjects with available brain tissue and 10 healthy volunteers. The SUVR were determined as a quantitative measure of tracer uptake. The SUV is defined as the ratio of the tissue radioactivity concentration c (in MBq/kg) at time point t, and the injected activity (in MBq), extrapolated to the same time (t) divided by the body weight (in kg). SUV numbers were then used to derive SUV ratios (SUVR) using the SUV from the cerebellar cortex as reference. SOTs comprised Bielschowsky silver staining (SOT 1), Bielschowsky silver staining with immunohistochemistry (SOT 2) and neuropathology assessment according to CERAD (SOT 3). SUVR analysis was performed for baseline and available follow-up scans. The optimal threshold for the distinction between β -amyloid present yes/no according to the respective SOT was derived based on ROC curve analyses and used to calculate Sensitivity and Specificity.	
End point type	Post-hoc
End point timeframe:	
90-110 minutes post injection (PET image acquisition).	

End point values	Final Analysis-Whole Brain			
Subject group type	Subject analysis set			
Number of subjects analysed	96 ^[3]			
Units: Sensitivity [%]				
number (not applicable)				
SOT 1 (initial period)	89			
SOT 2 (initial period)	90			
SOT 3 (initial period)	89			
SOT 1 (last available scan)	88			
SOT 2 (last available scan)	89			
SOT 3 (last available scan)	95			

Notes:

[3] - One subject not evaluable.

Statistical analyses

No statistical analyses for this end point

Post-hoc: Specificity of Subject Level Composite SUVR by SOT

End point title	Specificity of Subject Level Composite SUVR by SOT
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End point description:

Sensitivity and Specificity of subject level composite Standard Uptake Value Ratios (SUVR) by SOT for subjects with available brain tissue and 10 healthy volunteers. The SUVR were determined as a quantitative measure of tracer uptake. The SUV is defined as the ratio of the tissue radioactivity concentration c (in MBq/kg) at time point t , and the injected activity (in MBq), extrapolated to the same time (t) divided by the body weight (in kg). SUV numbers were then used to derive SUV ratios (SUVR) using the SUV from the cerebellar cortex as reference. SOTs comprised Bielschowsky silver staining (SOT 1), Bielschowsky silver staining with immunohistochemistry (SOT 2) and neuropathology assessment according to CERAD (SOT 3). SUVR analysis was performed for baseline and available follow-up scans. The optimal threshold for the distinction between β -amyloid present yes/no according to the respective

SOT was derived based on ROC curve analyses and used to calculate Sensitivity and Specificity

End point type	Post-hoc
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End point timeframe:

90-110 minutes post injection (PET image acquisition).

End point values	Final Analysis-Whole Brain			
Subject group type	Subject analysis set			
Number of subjects analysed	96 ^[4]			
Units: Specificity [%]				
number (not applicable)				
SOT 1 (initial period)	82			
SOT 2 (initial period)	91			
SOT 3 (initial period)	90			
SOT 1 (last available scan)	85			
SOT 2 (last available scan)	94			
SOT 3 (last available scan)	87			

Notes:

[4] - One subject was not evaluable.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All treatment emergent adverse events were recorded within 7 days of the application or follow-up application of study drug.

Adverse event reporting additional description:

As this study was conducted in an end-of-life population, death occurring outside 7 day follow-up period after administration of the drug, was not collected as part of the study SAE data unless investigator considered the event to be related to drug administration or study procedure. None of the SAEs reported was causally related to the treatment.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Initial Drug administration
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Reporting group description:

Subjects with TEAEs within 7 days of the initial administration of florbetaben.

Reporting group title	1st Repeat Drug Administration
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Reporting group description:

Subjects with TEAEs within 7 days of the 1st repeat drug administration.

Reporting group title	2nd Repeat Drug Administration
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Reporting group description:

Subjects with TEAEs within 7 days of the 2nd repeat drug administration.

Serious adverse events	Initial Drug administration	1st Repeat Drug Administration	2nd Repeat Drug Administration
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 216 (5.56%)	0 / 91 (0.00%)	0 / 34 (0.00%)
number of deaths (all causes)	88	20	3
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Pubis fracture			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences casually related to treatment / all	0 / 1	0 / 0	0 / 0
deaths casually related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences casually related to treatment / all	0 / 1	0 / 0	0 / 0
deaths casually related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Respiratory failure			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences casually related to treatment / all	0 / 1	0 / 0	0 / 0
deaths casually related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences casually related to treatment / all	0 / 1	0 / 0	0 / 0
deaths casually related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia Alzheimer's type			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences casually related to treatment / all	0 / 1	0 / 0	0 / 0
deaths casually related to treatment / all	0 / 1	0 / 0	0 / 0
Frontotemporal dementia			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences casually related to treatment / all	0 / 1	0 / 0	0 / 0
deaths casually related to treatment / all	0 / 1	0 / 0	0 / 0
General disorders and administration site conditions			
Heat stroke			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences casually related to treatment / all	0 / 1	0 / 0	0 / 0
deaths casually related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences casually related to treatment / all	0 / 1	0 / 0	0 / 0
deaths casually related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences casually related to treatment / all	0 / 1	0 / 0	0 / 0
deaths casually related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (0.00%)

occurrences casually related to treatment / all	0 / 1	0 / 0	0 / 0
deaths casually related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences casually related to treatment / all	0 / 1	0 / 0	0 / 0
deaths casually related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic cancer metastatic			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences casually related to treatment / all	0 / 1	0 / 0	0 / 0
deaths casually related to treatment / all	0 / 1	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences casually related to treatment / all	0 / 1	0 / 0	0 / 0
deaths casually related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences casually related to treatment / all	0 / 1	0 / 0	0 / 0
deaths casually related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences casually related to treatment / all	0 / 1	0 / 0	0 / 0
deaths casually related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences casually related to treatment / all	0 / 1	0 / 0	0 / 0
deaths casually related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Initial Drug administration	1st Repeat Drug Administration	2nd Repeat Drug Administration
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 216 (22.22%)	22 / 91 (24.18%)	14 / 34 (41.18%)
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 216 (0.46%)	5 / 91 (5.49%)	6 / 34 (17.65%)
occurrences (all)	1	5	6
Hypertension			
subjects affected / exposed	5 / 216 (2.31%)	1 / 91 (1.10%)	1 / 34 (2.94%)
occurrences (all)	5	1	1
Hypotension			
subjects affected / exposed	3 / 216 (1.39%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences (all)	3	0	0
Injury, poisoning and procedural complications			
Procedural hypertension			
subjects affected / exposed	0 / 216 (0.00%)	0 / 91 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	0 / 216 (0.00%)	1 / 91 (1.10%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood pressure increased			
subjects affected / exposed	3 / 216 (1.39%)	1 / 91 (1.10%)	0 / 34 (0.00%)
occurrences (all)	3	1	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 216 (0.00%)	0 / 91 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Emphysema			
subjects affected / exposed	0 / 216 (0.00%)	0 / 91 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 216 (1.39%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences (all)	3	0	0
General disorders and administration site conditions			

Injection site bruising subjects affected / exposed occurrences (all)	5 / 216 (2.31%) 5	0 / 91 (0.00%) 0	0 / 34 (0.00%) 0
Injection site erythema subjects affected / exposed occurrences (all)	4 / 216 (1.85%) 4	0 / 91 (0.00%) 0	1 / 34 (2.94%) 1
Injection site haematoma subjects affected / exposed occurrences (all)	10 / 216 (4.63%) 10	1 / 91 (1.10%) 1	0 / 34 (0.00%) 0
Injection site haemorrhage subjects affected / exposed occurrences (all)	1 / 216 (0.46%) 1	4 / 91 (4.40%) 4	2 / 34 (5.88%) 2
Injection site pain subjects affected / exposed occurrences (all)	4 / 216 (1.85%) 4	0 / 91 (0.00%) 0	0 / 34 (0.00%) 0
Puncture site reaction subjects affected / exposed occurrences (all)	7 / 216 (3.24%) 7	4 / 91 (4.40%) 4	0 / 34 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	7 / 216 (3.24%) 8	2 / 91 (2.20%) 2	0 / 34 (0.00%) 0
Vessel puncture site swelling subjects affected / exposed occurrences (all)	1 / 216 (0.46%) 1	1 / 91 (1.10%) 1	1 / 34 (2.94%) 1
Gastrointestinal disorders Frequent bowel movements subjects affected / exposed occurrences (all)	1 / 216 (0.46%) 1	1 / 91 (1.10%) 1	0 / 34 (0.00%) 0
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	1 / 216 (0.46%) 1	4 / 91 (4.40%) 5	3 / 34 (8.82%) 3
Haemorrhage subcutaneous subjects affected / exposed occurrences (all)	1 / 216 (0.46%) 1	3 / 91 (3.30%) 3	1 / 34 (2.94%) 1
Papule subjects affected / exposed	0 / 216 (0.00%)	1 / 91 (1.10%)	0 / 34 (0.00%)

occurrences (all)	0	1	0
Rash			
subjects affected / exposed	2 / 216 (0.93%)	1 / 91 (1.10%)	0 / 34 (0.00%)
occurrences (all)	3	1	0
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 216 (0.00%)	0 / 91 (0.00%)	1 / 34 (2.94%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2009	<ul style="list-style-type: none">Local amendment for Japan only.FDG PET imaging supplementary efficacy variablesChanges to meet Japanese specific GCP requirements
03 June 2010	<ul style="list-style-type: none">Duration of screening periodDescription of subject recruitment sourcesExclusion criterion 6 – Radiation exposureExclusion criterion 6 – More rapid enrollmentUse of a MRI performed outside the studyBiomarkersinjection procedureAutopsy and histopathology evaluation of brainsUse of the Boston Naming TestDescription of drug product characteristics and formulation
28 September 2010	<ul style="list-style-type: none">Title Page - Change in the name of the Study Medical Expert and one of the AuthorsSynopsis - Study Design - Change in the wordingSection 4.1.1.1 Inclusion criteria for the additional 10 negative controls only – Change in criteria 10Change in Exclusion Criteria #1 and #7Yearly follow-up visits (amended)Editorial change in Table 4
08 December 2010	<ul style="list-style-type: none">A new inclusion criterion (no. 8) was added.Statistical evaluation has been revised according to the recommendation made by FDA during the Type C meeting relating to the study-specific SAP.In addition minor changes to the protocol were made: Correction of some mistakes eg, forgotten to adopt the corrections made in Amendment 3 and to correct the description of the non-demented volunteers, which are not healthy subjects .
17 October 2011	<ul style="list-style-type: none">Secondary objectivesAdministration of the commercial formulationRelated to the audit functionPET scan visual assessment algorithmClarification that the 3-year follow-up was not mandatorySeveral other (additional) minor editorial changes
06 December 2012	<ul style="list-style-type: none">Change of sponsorChange of sponsor's medical expertChange of study administrative structureChange of subsection "Actions and reporting obligations in case of serious adverse events" within section Serious adverse eventsChange of section Monitoring

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25741488>

<http://www.ncbi.nlm.nih.gov/pubmed/25824567>

EudraCT - results validation report

EudraCT number: 2009-012569-79

Date and time: 16:14:03 30-June-2015

Trial Information

No errors or warnings found.

Subject Disposition

Pre-assignment period

WARNING: The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 35 subjects were screening failures and 2 subjects were never treated.

Period: Safety Analysis Set

WARNING: 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: Two patients were excluded from this population because injection of florbetaben was not done.

Baseline Characteristics

No errors or warnings found.

End Points

End Point: Sensitivity (Primary Efficacy Analysis)

WARNING: 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: The statistical analysis is provided as separate attachment.

End Point: Specificity (Primary Efficacy Analysis)

WARNING: 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: The statistical analysis is provided as separate attachment.

Adverse Events

No errors or warnings found.

More Information

No errors or warnings found.

Statistical Analysis for Sensitivity of the Majority Read of Visual Assessment of Tracer Uptake Compared to Histological Verification of the Presence or Absence of Cerebral Beta-amyloid in Postmortem Specimens

Statistical Analysis Overview	Comparison Groups	Sensitivity (Interim Analysis Set)
	Comments	<p>For the primary analysis, point estimates together with normal-approximated, two sided 95% confidence intervals, were given for sensitivity in beta-amyloid detection based on the majority read.</p> <p>The following hypothesis was formulated for sensitivity:</p> <p>$H_{0,sens}: \text{sensitivity} \leq 0.6$ vs. $H_1, \text{sens}: \text{sensitivity} > 0.6$ $H_{0,sens}$ was to be rejected if the lower bound of the two-sided 95% CI is larger than 0.6</p>
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Other [Sensitivity]
	Estimated Value	0.774
	Confidence Interval	(2-Sided) 95% 0.654 to 0.894
	Estimation Comments	Point estimate of sensitivity was calculated by the method of Rao and Scott. Variance for sensitivity is based on subjects that contribute at least one brain region, which is amyloid positive according to the SoT

Statistical Analysis for Specificity of the Majority Read of Visual Assessment of Tracer Uptake Compared to Histological Verification of the Presence or Absence of Cerebral Beta-amyloid in Postmortem Specimens

Statistical Analysis Overview	Comparison Groups	Specificity (Interim Analysis Set)
	Comments	<p>For the primary analysis, point estimates together with normal-approximated, two sided 95% confidence intervals, were given for specificity in amyloid detection based on the majority read.</p> <p>The following hypothesis was formulated for specificity:</p> <p>$H_{0,spec}: \text{specificity} \leq 0.8$ vs. $H_1, spec: \text{specificity} > 0.8$ $H_{0,spec}$ was to be rejected if the lower bound of the two-sided 95% CI is larger than 0.8</p>
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Specificity]
	Estimated Value	0.942
	Confidence Interval	(2-Sided) 95% 0.886 to 0.998
	Estimation Comments	Point estimate of specificity was calculated using the method of Rao and Scott. Variance for specificity is based on subjects that contribute at least one brain region, which is amyloid negative according to the SoT