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 ß-amyloid when compared to postmortem histopathology

Summary

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

Results information

Result version number	v1 (current)
This version publication date	01 March 2016
First version publication date	16 July 2015
Summary attachment (see zip file)	Combined File including all EudraCT files and statistics (EudraCT_Phase3_combined_final.pdf)

Trial information

Trial identification

Sponsor protocol code	BAY94-9172/14595

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

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

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
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.

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

Statistical analyses

No statistical analyses for this end point

Primary: Specificity (Primary Efficacy Analysis)

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

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:

[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

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)

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

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)

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

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[4]			
Units: Specificty [%]				
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

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Initial Drug administration

Reporting group description:

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

Reporting group title	1st Repeat Drug Administration

Reporting group description:

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

Reporting group title	2nd Repeat Drug Administration

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 causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally 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 causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally 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 causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally 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 causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally 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 causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally 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 causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally 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 causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally 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 causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally 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 causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally 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 causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally 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 causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (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
Spinal compression fracture			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 216 (0.46%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally 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 causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally 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%)
Investigations			
Blood pressure increased			
subjects affected / exposed	3 / 216 (1.39%)	1 / 91 (1.10%)	0 / 34 (0.00%)
occurrences (all)	3	1	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
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
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	5 / 216 (2.31%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences (all)	5	0	0
Injection site erythema			
subjects affected / exposed	4 / 216 (1.85%)	0 / 91 (0.00%)	1 / 34 (2.94%)
occurrences (all)	4	0	1
Injection site haematoma			

subjects affected / exposed	10 / 216 (4.63%)	1 / 91 (1.10%)	0 / 34 (0.00%)
occurrences (all)	10	1	0
Injection site haemorrhage			
subjects affected / exposed	1 / 216 (0.46%)	4 / 91 (4.40%)	2 / 34 (5.88%)
occurrences (all)	1	4	2
Injection site pain			
subjects affected / exposed	4 / 216 (1.85%)	0 / 91 (0.00%)	0 / 34 (0.00%)
occurrences (all)	4	0	0
Puncture site reaction			
subjects affected / exposed	7 / 216 (3.24%)	4 / 91 (4.40%)	0 / 34 (0.00%)
occurrences (all)	7	4	0
Pyrexia			
subjects affected / exposed	7 / 216 (3.24%)	2 / 91 (2.20%)	0 / 34 (0.00%)
occurrences (all)	8	2	0
Vessel puncture site swelling			
subjects affected / exposed	1 / 216 (0.46%)	1 / 91 (1.10%)	1 / 34 (2.94%)
occurrences (all)	1	1	1
Gastrointestinal disorders			
Frequent bowel movements			
subjects affected / exposed	1 / 216 (0.46%)	1 / 91 (1.10%)	0 / 34 (0.00%)
occurrences (all)	1	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
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 216 (0.46%)	4 / 91 (4.40%)	3 / 34 (8.82%)
occurrences (all)	1	5	3
Haemorrhage subcutaneous			
subjects affected / exposed	1 / 216 (0.46%)	3 / 91 (3.30%)	1 / 34 (2.94%)
occurrences (all)	1	3	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	Local amendment for Japan only. • FDG PET imaging supplementary efficacy variables • Changes to meet Japanese specific GCP requirements
03 June 2010	• Duration of screening period • Description of subject recruitment sources • Exclusion criterion 6 – Radiation exposure • Exclusion criterion 6 – More rapid enrollment • Use of a MRI performed outside the study • Biomarkers • injection procedure • Autopsy and histopathology evaluation of brains • Use of the Boston Naming Test • Description of drug product characteristics and formulation
28 September 2010	• Title Page - Change in the name of the Study Medical Expert and one of the Authors • Synopsis - Study Design - Change in the wording • Section 4.1.1.1 Inclusion criteria for the additional 10 negative controls only – Change in criteria 10 • Change in Exclusion Criteria #1 and #7 • Yearly follow-up visits (amended) • Editorial change in Table 4
08 December 2010	• 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	• Secondary objectives • Administration of the commercial formulation • Related to the audit function • PET scan visual assessment algorithm • Clarification that the 3-year follow-up was not mandatory • Several other (additional) minor editorial changes
06 December 2012	• Change of sponsor • Change of sponsor’s medical expert • Change of study administrative structur • Change of subsection “Actions and reporting obligations in case of serious adverse events” within section Serious adverse events • Change 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