Clinical trial results:
A randomized, multicenter, multicountry study to evaluate the effectiveness of Florbetapir (18F) PET imaging in changing patient management and to evaluate the relationship between Florbetapir (18F) PET status and cognitive decline.

Summary

EudraCT number	2012-002595-13
Trial protocol	IT
Global end of trial date	02 April 2015

Results information

Result version number	v1 (current)
This version publication date	29 April 2016
First version publication date	29 April 2016

Trial information

Trial identification

Sponsor protocol code	18F-AV-45-A18

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01703702
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Avid Radiopharmaceuticals, Inc.
Sponsor organisation address	3711 Market St., Philadelphia, United States, 19104
Public contact	Clinical Operations, Avid Radiopharmaceuticals, 1 215 2980700,
Scientific contact	Chief Medical Officer, Avid Radiopharmaceuticals, 1 215 2980700,

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	02 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 April 2015
Global end of trial reached?	Yes
Global end of trial date	02 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Patient Management: To evaluate the effectiveness of florbetapir (18F) PET imaging in changing patient management, as defined by the treating physician. Change in management will be determined by comparing the intended management (pre-scan) to the observed management (during the 3 months following the scan).

Patient Prognosis: To evaluate the association between scan status and cognitive decline as measured by Alzheimer's Disease Assessment Scale —Cognitive subscale (ADAS-cog) in study patients with mild impairment of cognition .

Protection of trial subjects:

Subjects who received florbetapir (18F) were closely followed by means of adverse event reporting and vital signs. In the event of a study related adverse event, subjects would not have been discharged until the event had resolved or stabilized. Subjects were made aware of the planned procedures and their comfort in the scanner was maximized to minimize the risk of any discomfort while in the PET scanner.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 November 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	France: 178
Country: Number of subjects enrolled	Italy: 231
Country: Number of subjects enrolled	United States: 232
Worldwide total number of subjects	641
EEA total number of subjects	409

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)	100
From 65 to 84 years	502
85 years and over	39

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

641 patients were enrolled in the study. 21 of these subjects did not receive florbetapir (18F). 620 patients received florbetapir (18F) and comprise the Safety Population. Of the patients who received florbetapir (18F), 2 patients did not have a successful PET scan. The remaining 618 patients comprise the Efficacy Population.

Pre-assignment period milestones

Number of subjects started	641
Intermediate milestone: Number of subjects	Safety Population: 620
Number of subjects completed	618

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 5
Reason: Number of subjects	Hospitalized for pneumonia: 1
Reason: Number of subjects	Diagnosed with lung cancer: 1
Reason: Number of subjects	Death: 1
Reason: Number of subjects	Food allergic reaction: 1
Reason: Number of subjects	Consent withdrawn: 9
Reason: Number of subjects	Subject decided to stop the study: 1
Reason: Number of subjects	Caregiver not able to accompany patient: 1
Reason: Number of subjects	Unable to complete PET scan: 2
Reason: Number of subjects	Hospitalized for seizures: 1

Period 1

Period 1 title	Efficacy Population (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Subject, Investigator, Carer, Assessor

Blinding implementation details:

All patients received florbetapir (18F). Interventional group: the treating physician, patient, and caregiver were informed of the florbetapir (18F) PET scan results. Control group: the treating physician, patient, and caregiver were blinded to the florbetapir (18F) PET scan result for a period of 12 months. Raters administering the ADAS-Cog were blinded to PET scan results for all patients. Physicians who interpreted the PET scans were blinded to all other clinical information.

Arms

Are arms mutually exclusive?	Yes

Arm title	Interventional

Arm description:

The treating physician, patient and caregiver were informed of the result of the florbetapir (18F) PET.

Arm type	Experimental
Investigational medicinal product name	Florbetapir (18F)
Investigational medicinal product code	18F-AV-45
Other name	Amyvid, florbetapir F 18
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received a one-time intravenous (IV) bolus injection of 370 megabecquerels (MBq) florbetapir (18F).

Arm title	Control

Arm description:

The treating physician, patient and caregiver were blinded the result of the florbetapir (18F) PET scan for a period of 12 months.

Arm type	Experimental
Investigational medicinal product name	Florbetapir (18F)
Investigational medicinal product code	18F-AV-45
Other name	Amyvid, florbetapir F 18
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received a one-time intravenous (IV) bolus injection of 370 megabecquerels (MBq) florbetapir (18F).

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Please see the blinding implementation details as the blinding in this study is not related to the typical treatment/placebo paradigm.

Number of subjects in period 1[2]	Interventional	Control
Started	308	310
Completed	272	288
Not completed	36	22
Caregiver hospitalized, patient institutionalized	1	-
Physical/Cognitive impairment prevent consultation	1	-
Behavioral disturbance	-	1
Administrative Decision	5	5
Patient wanted PET scan results before 12 months	-	3
Patient noncompliant for tests	1	-
Patient moved	-	1
Patient decision	1	-
Consent withdrawn by subject	13	5
Screening failure	-	1
Concurrent motorneuron disease	1	-

Ischemic stroke	-	1
Death	2	3
Broken hip, unable to return for final visit	-	1
Hospitalized on life support	1	-
Lost to follow-up	4	1
Patient erroneously indicated as screen failure	1	-
Inclusion in a clinical trial	5	-

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: Refer to the pre-assignment period for details on the subjects who enrolled in the study but were not randomized to the baseline Efficacy Population.

Baseline characteristics

Reporting groups	
Reporting group title	Interventional
Reporting group description:	
The treating physician, patient and caregiver were informed of the result of the florbetapir (18F) PET.	
Reporting group title	Control
Reporting group description:	
The treating physician, patient and caregiver were blinded the result of the florbetapir (18F) PET scan for a period of 12 months.	

Reporting group values	Interventional	Control	Total
Number of subjects	308	310	618
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	73.1	72.7	
standard deviation	± 8.2	± 7.94	-
Gender categorical			
Units: Subjects			
Female	142	160	302
Male	166	150	316

End points

End points reporting groups

Reporting group title	Interventional
Reporting group description:	
The treating physician, patient and caregiver were informed of the result of the florbetapir (18F) PET.	
Reporting group title	Control
Reporting group description:	
The treating physician, patient and caregiver were blinded the result of the florbetapir (18F) PET scan for a period of 12 months.	
Subject analysis set title	Mild Impairment AB+
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients diagnosed with a cognitive status of mild impairment and AB+ scan result.	
Subject analysis set title	Mild Impairment AB-
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients diagnosed with a cognitive status of mild impairment and AB- scan result.	
Subject analysis set title	Intervention scan/diagnosis discordant
Subject analysis set type	Per protocol
Subject analysis set description:	
Intervention arm patients whose florbetapir F18 PET scan results that were not predicted by their baseline clinical diagnosis.	
Subject analysis set title	Control scan/diagnosis discordant
Subject analysis set type	Per protocol
Subject analysis set description:	
Control arm patients whose florbetapir F18 PET scan results that were not predicted by their baseline clinical diagnosis.	
Subject analysis set title	Intervention scan/diagnosis concordant
Subject analysis set type	Per protocol
Subject analysis set description:	
Intervention arm patients whose F18 PET scan results were predicted by their initial diagnosis	
Subject analysis set title	Control scan/diagnosis concordant
Subject analysis set type	Per protocol
Subject analysis set description:	
Control arm patients whose F18 PET scan results were predicted by their initial diagnosis	

Primary: Clinical and Diagnostic Change in Patient Management

End point title	Clinical and Diagnostic Change in Patient Management
End point description:	
Comparison of the percentage of patients who have a change in management from baseline to 3 months for patients who receive scan results immediately (intervention arm) and those who receive scan results 12 months later (control arm).	
End point type	Primary
End point timeframe:	
3 months	

End point values	Interventional	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	300	299		
Units: percentage of patients				
number (not applicable)				
Change	68	55.5		

Statistical analyses

Statistical analysis title	Primary Objective 1
Comparison groups	Control v Interventional
Number of subjects included in analysis	599
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.22
upper limit	2.38

Primary: Change in ADAS-Cog 11 Total Score

End point title	Change in ADAS-Cog 11 Total Score

End point description:

Change from baseline in the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog) 11 Score in patients with mild impairment by positive or negative florbetapir (18F) PET scan result (Aß+/Aß-).

End point type	Primary

End point timeframe:

12 months

End point values	Mild Impairment AB+	Mild Impairment AB-		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	178	134		
Units: ADAS-Cog 11				
least squares mean (standard error)				
Change from Baseline	0.95 (± 0.38)	1.29 (± 0.43)		

Statistical analyses

Statistical analysis title	Primary Objective 2
Comparison groups	Mild Impairment AB+ v Mild Impairment AB-
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.568 [1]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.54
upper limit	0.84

Notes:

[1] - ANCOVA adjusted for confounding factors: Baseline ADAS-Cog score, study arm, Alzheimer's treatment, country, and interaction between study arm and Alzheimer's treatment.

Secondary: Change in Patient's Clinical Diagnosis

End point title	Change in Patient's Clinical Diagnosis

End point description:

Comparison of the percentage of patients who have a change in diagnosis from baseline to 3 months for patients in the intervention and control arms for whom the scan result was not predicted by the initial diagnosis.

End point type	Secondary

End point timeframe:

3 months

End point values	Intervention scan/diagnosis discordant	Control scan/diagnosis discordant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	111	109		
Units: percentage of patients				
number (not applicable)				
Change	85.6	11.9		

Statistical analyses

Statistical analysis title	Secondary Objective 1
Comparison groups	Intervention scan/diagnosis discordant v Control scan/diagnosis discordant
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	43.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	20
upper limit	96.12

Secondary: Change in Diagnostic Confidence

End point title	Change in Diagnostic Confidence

End point description:

Comparison of the percentage point change in the physician's diagnostic confidence from baseline to month 3 in the intervention and control arms for patients whose scan result was predicted by their baseline clinical diagnosis.

End point type	Secondary

End point timeframe:

3 months

End point values	Intervention scan/diagnosis concordant	Control scan/diagnosis concordant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	189	190		
Units: Percentage Point				
least squares mean (standard error)				
Change	23.54 (± 1.13)	2.85 (± 1.15)		

Statistical analyses

Statistical analysis title	Secondary Objective 2
Comparison groups	Intervention scan/diagnosis concordant v Control scan/diagnosis concordant

Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	20.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.95
upper limit	22.43

Secondary: Change in Patient Management: Advice/Counseling

End point title	Change in Patient Management: Advice/Counseling

End point description:

Comparison of the percentage of patients in the intervention and control arms who have a change in management relating to advice and counseling from baseline to 3 months.

End point type	Secondary

End point timeframe:

3 months

End point values	Interventional	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	300	299		
Units: percentage of patients				
number (not applicable)				
Change	64.7	58.9		

Statistical analyses

Statistical analysis title	Secondary Objective 3
Comparison groups	Control v Interventional
Number of subjects included in analysis	599
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.144
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.78

Secondary: Change in Caregiver Self-efficacy

End point title	Change in Caregiver Self-efficacy

End point description:

Comparison of the change in self-efficacy between intervention and control arms. Change in self-efficacy is defined as the difference between total score on the Fortinsky: Family caregivers' self-efficacy for managing dementia scale at Follow-up (3 months) and baseline.

End point type	Secondary

End point timeframe:

3 months

End point values	Interventional	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	297		
Units: score				
least squares mean (standard error)				
Change	0.16 (± 1.24)	0 (± 1.26)		

Statistical analyses

Statistical analysis title	Secondary Objective 4
Comparison groups	Interventional v Control
Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.925
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	3.53

Secondary: Change in Patient Management: Individual Categories

End point title	Change in Patient Management: Individual Categories

End point description:

Compare the percentage of patients with a change from baseline in the individual patient management categories at 3 months in the interventional and control arms.The individual categories are: Major diagnostic tests, Alzheimer's/cognition medication, neuropsychological tests, physician follow-up for re-evaluation or specialist referral.

End point type	Secondary

End point timeframe:

3 months

End point values	Interventional	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	300	299		
Units: percentage of patients				
number (not applicable)				
Major Diagnostic Tests	21	20.4		
Alzheimer's/Cognitive Medication	35.7	22.1		
Neuropsychological Tests	14.7	9.7		
Physician Follow-up for Re-evaluation	15	14		
Specialist Referral	30.7	23.4		

Statistical analyses

Statistical analysis title	Major Diagnostic Tests
Comparison groups	Interventional v Control
Number of subjects included in analysis	599
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.857
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.54

Statistical analysis title	Alzheimer's/Cognitive Medication
Comparison groups	Interventional v Control

Number of subjects included in analysis	599
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.36
upper limit	2.81

Statistical analysis title	Neuropsychological Tests
Comparison groups	Interventional v Control
Number of subjects included in analysis	599
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.063
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	2.64

Statistical analysis title	Physician Follow-up for Re-evaluation
Comparison groups	Interventional v Control
Number of subjects included in analysis	599
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.741
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.7

Statistical analysis title	Specialist Referral

Comparison groups	Interventional v Control
Number of subjects included in analysis	599
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.046
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	2.08

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 48 hours post-injection	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0
Reporting groups	
Reporting group title	Safety Population
Reporting group description: All subjects	

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 620 (0.32%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 620 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 620 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 620 (5.81%)		
Injury, poisoning and procedural complications			

Post procedural haematoma subjects affected / exposed occurrences (all)	1 / 620 (0.16%) 1		
Vascular disorders Flushing subjects affected / exposed occurrences (all)	1 / 620 (0.16%) 1		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	1 / 620 (0.16%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	17 / 620 (2.74%) 17 1 / 620 (0.16%) 1		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Feeling abnormal subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all)	3 / 620 (0.48%) 3 3 / 620 (0.48%) 3 1 / 620 (0.16%) 1 1 / 620 (0.16%) 1		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 620 (0.16%) 1		
Gastrointestinal disorders			

Nausea subjects affected / exposed occurrences (all) Abnormal faeces subjects affected / exposed occurrences (all)	4 / 620 (0.65%) 4 1 / 620 (0.16%) 1		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	1 / 620 (0.16%) 1		
Psychiatric disorders Confusional state subjects affected / exposed occurrences (all) Hallucination, olfactory subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Irritability subjects affected / exposed occurrences (all) Sleep disorder subjects affected / exposed occurrences (all)	1 / 620 (0.16%) 1 1 / 620 (0.16%) 1 1 / 620 (0.16%) 1 1 / 620 (0.16%) 1 1 / 620 (0.16%) 1		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	1 / 620 (0.16%) 1		
Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all) Myalgia	1 / 620 (0.16%) 1		

subjects affected / exposed occurrences (all)	1 / 620 (0.16%) 1		
Infections and infestations Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	 1 / 620 (0.16%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2013	The primary purpose of amendment 1 was to group all objectives determined at the 3 month time point as secondary objectives, to remove QoL-AD as an assessment for patient's caregivers because it is a measure for patients, and to restructure the 12 month visit to include a pre-visit and a clinic visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported