Clinical trial results:
A Phase 2b/3 Randomized, Double-blind, Placebo-Controlled, Parallel Group, Multicenter Study Investigating the Efficacy and Safety of JNJ-54861911 in Subjects who are Asymptomatic At Risk for Developing Alzheimer's Dementia

Summary

EudraCT number	2015-000948-42
Trial protocol	SE DE DK BE ES FI NL IT
Global end of trial date	20 December 2018

Results information

Result version number	v1 (current)
This version publication date	05 January 2020
First version publication date	05 January 2020

Trial information

Trial identification

Sponsor protocol code	54861911ALZ2003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02569398
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202, Raritan, United States, NJ 08869
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.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	20 December 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 December 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to determine whether treatment with atabecestat slows cognitive decline compared with placebo treatment, as measured by a composite cognitive measure, the Preclinical Alzheimer Cognitive Composite (PACC), in amyloid-positive subjects who were asymptomatic at risk for developing Alzheimer's dementia.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and applicable regulatory requirements. The safety assessments included adverse events, clinical laboratory tests, electrocardiograms, vital signs, physical examination body weight measurements; Magnetic resonance imaging (MRI), centrally read; and physical, neurological, and dermatological examinations and psychometric assessments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 November 2015
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	Australia: 63
Country: Number of subjects enrolled	Belgium: 28
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Denmark: 60
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	United Kingdom: 67
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Japan: 33
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Netherlands: 31
Country: Number of subjects enrolled	Sweden: 12
Country: Number of subjects enrolled	United States: 199
Worldwide total number of subjects	557
EEA total number of subjects	246

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)	86
From 65 to 84 years	470
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total of 557 subjects were enrolled in study. Study was early terminated based on experience of significant elevations in liver enzymes in subjects receiving JNJ-54861911 in this study and 54861911ALZ2004 (NCT02406027).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received a single dose of JNJ-54861911 matching placebo tablet orally once daily for up to 24 months.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of atabecestat matching placebo tablet orally once daily for up to 54 months.

Arm title	JNJ-54861911 (5 mg)

Arm description:

Subjects received a single dose of JNJ-54861911 5 milligram (mg) tablet orally once daily for up to 24 months (subjects randomized to this group received JNJ-54861911 10 mg prior to protocol amendment 3 and continued to receive JNJ-54861911 5-mg tablets after implementation of protocol Amendment 3; dated: 02-Mar-2016).

Arm type	Experimental
Investigational medicinal product name	JNJ-54861911
Investigational medicinal product code	
Other name	Atabecestat
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of atabecestat 5 mg tablet orally once daily for up to 54 months.

Investigational medicinal product name	JNJ-54861911
Investigational medicinal product code	
Other name	Atabecestat
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of atabecestat 10 mg tablet orally once daily for up to 54 months.

Arm title	JNJ-54861911 (25 mg)

Arm description:

Subjects received a single dose of JNJ-54861911 25 mg tablet orally once daily for up to 24 months.

Arm type	Experimental
Investigational medicinal product name	JNJ-54861911
Investigational medicinal product code	
Other name	Atabecestat
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single dose of atabecestat 25 mg tablet orally once daily for up to 54 months.

Number of subjects in period 1	Placebo	JNJ-54861911 (5 mg)	JNJ-54861911 (25 mg)
Started	185	189	183
Completed	0	0	0
Not completed	185	189	183
Consent withdrawn by subject	43	43	30
Study terminated by sponsor	130	131	134
Adverse event	-	1	6
Unspecified	12	14	13

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received a single dose of JNJ-54861911 matching placebo tablet orally once daily for up to 24 months.	
Reporting group title	JNJ-54861911 (5 mg)
Reporting group description:	
Subjects received a single dose of JNJ-54861911 5 milligram (mg) tablet orally once daily for up to 24 months (subjects randomized to this group received JNJ-54861911 10 mg prior to protocol amendment 3 and continued to receive JNJ-54861911 5-mg tablets after implementation of protocol Amendment 3; dated: 02-Mar-2016).	
Reporting group title	JNJ-54861911 (25 mg)
Reporting group description:	
Subjects received a single dose of JNJ-54861911 25 mg tablet orally once daily for up to 24 months.	

Reporting group values	Placebo	JNJ-54861911 (5 mg)	JNJ-54861911 (25 mg)
Number of subjects	185	189	183
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	33	23	30
From 65 to 84 years	151	166	153
85 years and over	1	0	0
Title for AgeContinuous Units: years			
arithmetic mean	70.2	70.6	70.5
standard deviation	± 5.81	± 5.26	± 5.62
Title for Gender Units: subjects			
Female	108	116	117
Male	77	73	66
Title for Race Units: Subjects			
White	167	173	168
Black or African American	2	1	2
Asian	12	11	11
American Indian or Alaska Native	0	1	0
Other	4	3	2

Reporting group values	Total		
Number of subjects	557		
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	86		
From 65 to 84 years	470		

85 years and over	1		

Title for AgeContinuous Units: years arithmetic mean standard deviation	- 		
Title for Gender Units: subjects			
Female	341		
Male	216		
Title for Race Units: Subjects			
White	508		
Black or African American	5		
Asian	34		
American Indian or Alaska Native	1		
Other	9		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received a single dose of JNJ-54861911 matching placebo tablet orally once daily for up to 24 months.	
Reporting group title	JNJ-54861911 (5 mg)
Reporting group description:	
Subjects received a single dose of JNJ-54861911 5 milligram (mg) tablet orally once daily for up to 24 months (subjects randomized to this group received JNJ-54861911 10 mg prior to protocol amendment 3 and continued to receive JNJ-54861911 5-mg tablets after implementation of protocol Amendment 3; dated: 02-Mar-2016).	
Reporting group title	JNJ-54861911 (25 mg)
Reporting group description:	
Subjects received a single dose of JNJ-54861911 25 mg tablet orally once daily for up to 24 months.	

Primary: Change from Baseline in Preclinical Alzheimer Cognitive Composite (PACC) Score at Endpoint (Month 24)

End point title	Change from Baseline in Preclinical Alzheimer Cognitive Composite (PACC) Score at Endpoint (Month 24)[1]
End point description:	
PACC has 4 components: Free and Cued Selective Reminding Test (0 (worst)-48 (best recall); Delayed Paragraph Recall test (Range 0 (worst)-25 (best recall); Wechsler Adult Intelligence scale: (ranges 0 [none]-135 [best performance]) and Mini Mental State Examination (Range 0 [worst]-30 [best performance]). Component scores are transformed using an established normalization method into z-scores. Each of 4 component change scores is divided by baseline sample standard deviation (SD) of that component. Z-score implies how many SD higher or lower score as compared with baseline score with increase signifying improvement. ITT analysis set with subjects in whom PACC change score is non-missing at>=1 post-baseline timepoint.	
End point type	Primary
End point timeframe:	
Baseline and Endpoint (Month 24)	

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Placebo	JNJ-54861911 (5 mg)	JNJ-54861911 (25 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	73	64	
Units: Score on a scale				
arithmetic mean (standard deviation)	0.096 (± 1.7261)	-0.417 (± 1.8372)	-1.096 (± 1.7796)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Cognitive Function Index (CFI) Score at Endpoint (Month 24)

End point title	Change from Baseline in Cognitive Function Index (CFI) Score at Endpoint (Month 24)

End point description:

The CFI is a modified version of the Mail-in Cognitive Function Screening Instrument, a subject- and informant-reported outcome measure developed by the Alzheimer's Disease Cooperative Study (ADCS). This assessment includes 15 questions (14 of which contribute to the total score, and 1 additional unscored item) that assess the subject's perceived ability to perform high-level functional tasks in daily-life and sense of overall cognitive functional ability. Study subjects and their informants independently rate the subject's abilities. Total scores range from 0 to 14 (yes=1; no=0; maybe=0.5 for each question) with higher scores indicating greater impairment. Intent to treat (ITT) analysis set included all randomized subjects. Here 'n' (number analyzed) was defined as the number of subjects evaluable at specified category.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Month 24)

End point values	Placebo	JNJ-54861911 (5 mg)	JNJ-54861911 (25 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	185	189	183	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Total CFI Participant score:Month 54(n=28,27,26)	-0.04 (± 1.866)	0.09 (± 1.135)	0.75 (± 2.628)	
Total CFI Informant score:Month 54(n=27,27,26)	-0.22 (± 1.660)	0.30 (± 1.469)	0.88 (± 2.475)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Alzheimer's Disease Cooperative Study - Activities of Daily Living - Prevention Instrument (ADCS-ADLPI) Total Score at Endpoint (Month 24)

End point title	Change from Baseline in Alzheimer's Disease Cooperative Study - Activities of Daily Living - Prevention Instrument (ADCS-ADLPI) Total Score at Endpoint (Month 24)

End point description:

The Alzheimer's Disease Cooperative Study - Activities of Daily Living -Prevention Instrument (ADCS-ADLPI) is a functional measure composed of 18 items that included 15 activities of daily living rated on a 4-point scale and 3 high level function items. Study subjects and their informants independently rate the subject's level of ability. Informants are additionally asked to evaluate whether activities were completed less often, required more time to complete, and if any errors were made performing the task. High-level function items are rated as "yes" or "no". The scores range from 0 to 45 with higher scores indicating less impairment. ITT analysis set included all randomized subjects. Here 'n' (number analyzed) was defined as the number of subjects evaluable at specified category.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Month 24)

End point values	Placebo	JNJ-54861911 (5 mg)	JNJ-54861911 (25 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	185	189	183	
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Total ADL Participant score: (n=124,117,110)	-0.04 (± 2.975)	0.35 (± 2.832)	0.15 (± 2.834)	
Total ADL Informant score (n= 122, 115, 109)	0.26 (± 4.223)	-0.12 (± 3.941)	0.24 (± 4.085)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Total Scale Score at Endpoint (Month 24)

End point title	Change from Baseline in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Total Scale Score at Endpoint (Month 24)

End point description:

RBANS is 20 to 25 minute battery developed for cognitive assessment, detection, and characterization of dementia. RBANS includes 12 subtests that measure following 5 indices: (1)Attention Index, composed of Digit Span and Coding; (2)Language Index, consisting of Picture Naming and Semantic Fluency subtests; (3)Visuospatial/Construction Index, made up of Figure Copy and Line Orientation subtests; (4)Immediate Memory Index, composed of List Learning and Story Memory subtests, and (5)Delayed Memory Index, consisting of List Recall, List Recognition, Story Recall, and Figure Recall subtests. Completion of RBANS yields 5 index scores based on subject performance on various subtests, as well as a composite Total Index score for battery. Index scores range from 40 to 160, and are normalized to a mean of 100 and standard deviation (SD) of 15. Higher scores indicate less impairment. ITT analysis set included. Here 'N' (number of subjects analyzed): subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Month 24)

End point values	Placebo	JNJ-54861911 (5 mg)	JNJ-54861911 (25 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124	121	114	
Units: Score on a scale				
arithmetic mean (standard deviation)	2.0 (± 8.90)	-0.9 (± 7.79)	-1.7 (± 9.75)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Clinical Dementia Rating - Sum of Boxes (CDR-SB) Score at Endpoint (Month 24)

End point title	Change from Baseline in Clinical Dementia Rating - Sum of Boxes (CDR-SB) Score at Endpoint (Month 24)

End point description:

The CDR-SB is an interviewer administered scale and impairment is scored in each of categories: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Impairment is scored on a scale in which none = 0, questionable = 0.5, mild = 1, moderate = 2 and severe = 3. The 6 individual category ratings, or "box scores", were added together to give the CDR-Sum of Boxes which ranges from 0-18. Higher score indicates severe impairment.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Month 24)

End point values	Placebo	JNJ-54861911 (5 mg)	JNJ-54861911 (25 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: Score on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[2] - Study terminated early due to less subjects, limited sample size. Data was not collected/analyzed.

[3] - Study terminated early due to less subjects, limited sample size. Data was not collected/analyzed.

[4] - Study terminated early due to less subjects, limited sample size. Data was not collected/analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Neuropsychological Assessment Battery Daily Living Tests (NABDLTs) Score at Endpoint (Month 24)

End point title	Change from Baseline in Neuropsychological Assessment Battery Daily Living Tests (NABDLTs) Score at Endpoint (Month 24)

End point description:

The Neuropsychological Assessment Battery Daily Living Tests (NABDLTs) Score represent a series of performance based measures covering 5 domains (Attention, Memory, Language, Spatial, and Executive function). These are valid, clinically meaningful measures that objectively assess functional deficits. Participant performance scores on NAB subtests are summed, and then normalized to yield an index score. Index scores can range from less than or equal to (< =) 55 to greater than or equal to (> =) 145, and are normalized to a mean of 100 and standard deviation of 15. Higher scores indicate less impairment.

End point type	Secondary

End point timeframe:

Baseline and Endpoint (Month 24)

End point values	Placebo	JNJ-54861911 (5 mg)	JNJ-54861911 (25 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[5]	0[6]	0[7]	
Units: Score on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[5] - Study terminated early due to less subjects, limited sample size. Data was not collected/analyzed.

[6] - Study terminated early due to less subjects, limited sample size. Data was not collected/analyzed.

[7] - Study terminated early due to less subjects, limited sample size. Data was not collected/analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 24 months	
Adverse event reporting additional description:	
Safety analysis set included all randomized subjects who have received at least one study medication.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received a single dose of JNJ-54861911 matching placebo tablet orally once daily for up to 24 months.	
Reporting group title	JNJ-54861911 (25 mg)
Reporting group description:	
Subjects received a single dose of JNJ-54861911 25 mg tablet orally once daily for up to 24 months.	
Reporting group title	JNJ-54861911 (5 mg)
Reporting group description:	
Subjects received a single dose of JNJ-54861911 5 milligram (mg) tablet orally once daily for up to 24 months (subjects randomized to this group received JNJ-54861911 10 mg prior to protocol amendment 3 and continued to receive JNJ-54861911 5-mg tablets after implementation of protocol Amendment 3; dated: 02-Mar-2016).	

Serious adverse events	Placebo	JNJ-54861911 (25 mg)	JNJ-54861911 (5 mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 185 (4.86%)	26 / 183 (14.21%)	18 / 189 (9.52%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of Colon			
subjects affected / exposed	0 / 185 (0.00%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign Ovarian Tumour			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Cancer			

subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast Cancer Metastatic			
subjects affected / exposed	0 / 185 (0.00%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Lymphocytic Leukaemia			
subjects affected / exposed	0 / 185 (0.00%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Stromal Tumour			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant Melanoma			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate Cancer			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	0 / 185 (0.00%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			

Benign Prostatic Hyperplasia			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejaculation Failure			
subjects affected / exposed	0 / 185 (0.00%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erectile Dysfunction			
subjects affected / exposed	0 / 185 (0.00%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthmatic Crisis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiectasis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emphysema			
subjects affected / exposed	0 / 185 (0.00%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Mass			
subjects affected / exposed	0 / 185 (0.00%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Loss of Libido			
subjects affected / exposed	0 / 185 (0.00%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Mental Status Changes			
subjects affected / exposed	0 / 185 (0.00%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 185 (0.00%)	2 / 183 (1.09%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 185 (0.00%)	3 / 183 (1.64%)	2 / 189 (1.06%)
occurrences causally related to treatment / all	0 / 0	3 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases Increased			
subjects affected / exposed	0 / 185 (0.00%)	2 / 183 (1.09%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	0 / 185 (0.00%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial Bones Fracture			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	0 / 189 (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
Femoral Neck Fracture			

subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured Ischium			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	0 / 189 (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
Post Lumbar Puncture Syndrome			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib Fracture			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	0 / 189 (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			
Angina Unstable			
subjects affected / exposed	0 / 185 (0.00%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	0 / 185 (0.00%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachyarrhythmia			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	0 / 189 (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
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Radiculopathy			

subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbosacral Radiculopathy			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	0 / 189 (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
Paralysis Recurrent Laryngeal Nerve			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Ischaemic Attack			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	0 / 189 (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
Eye disorders			
Cataract			
subjects affected / exposed	0 / 185 (0.00%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal Detachment			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Mechanical Ileus			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	0 / 189 (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			

Cholangitis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-Induced Liver Injury			
subjects affected / exposed	0 / 185 (0.00%)	3 / 183 (1.64%)	0 / 189 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 185 (0.00%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 185 (0.00%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	0 / 189 (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
Pneumonia			

subjects affected / exposed	0 / 185 (0.00%)	0 / 183 (0.00%)	1 / 189 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Poliomyelitis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	0 / 189 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	0 / 189 (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: 5 %

Non-serious adverse events	Placebo	JNJ-54861911 (25 mg)	JNJ-54861911 (5 mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 185 (43.24%)	88 / 183 (48.09%)	75 / 189 (39.68%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	9 / 185 (4.86%)	14 / 183 (7.65%)	9 / 189 (4.76%)
occurrences (all)	9	16	16
Aspartate Aminotransferase Increased			
subjects affected / exposed	8 / 185 (4.32%)	12 / 183 (6.56%)	9 / 189 (4.76%)
occurrences (all)	8	12	11
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 185 (7.57%)	16 / 183 (8.74%)	12 / 189 (6.35%)
occurrences (all)	16	19	15
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 185 (1.62%)	11 / 183 (6.01%)	5 / 189 (2.65%)
occurrences (all)	3	11	5
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	7 / 185 (3.78%)	28 / 183 (15.30%)	15 / 189 (7.94%)
occurrences (all)	9	34	18
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 185 (1.08%)	6 / 183 (3.28%)	12 / 189 (6.35%)
occurrences (all)	2	7	13
Psychiatric disorders			
Abnormal Dreams			
subjects affected / exposed	1 / 185 (0.54%)	11 / 183 (6.01%)	4 / 189 (2.12%)
occurrences (all)	1	12	4
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	9 / 185 (4.86%)	10 / 183 (5.46%)	11 / 189 (5.82%)
occurrences (all)	9	11	13
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	27 / 185 (14.59%)	16 / 183 (8.74%)	19 / 189 (10.05%)
occurrences (all)	35	21	26
Upper Respiratory Tract Infection			
subjects affected / exposed	19 / 185 (10.27%)	12 / 183 (6.56%)	14 / 189 (7.41%)
occurrences (all)	22	20	19
Urinary Tract Infection			
subjects affected / exposed	7 / 185 (3.78%)	15 / 183 (8.20%)	8 / 189 (4.23%)
occurrences (all)	7	18	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 June 2015	To add a risk-benefit statement to Section 1.3 (Target Population – Asymptomatic Subjects at Risk for Alzheimer's Dementia), amend a secondary endpoint, and remove the listing of anticipated events.
21 July 2015	To add an additional adverse event of special interest to Section 11.10 (Safety Analyses).
02 March 2016	To reduce the 10-mg treatment to 5-mg of JNJ-54861911, to add additional scales to the study, and to make other required changes which were relevant to the study.
31 May 2016	To provide clarification and extra safety precautions to the lumbar puncture procedures (for those subjects who were receiving lumbar punctures for cerebrospinal fluid [CSF] sampling).
24 March 2017	To add new monitoring guidelines and stopping rules for liver enzymes during the first 3 months of treatment and to provide additional information on the management of elevated liver enzymes, to remove previously prohibited concomitant medications, to remove the stated-choice preference study, to update the frequency of the Alzheimer's Disease Cooperative Study - Activities of Daily Living-Prevention Instrument (ADCS-ADL-PI), Cognitive Function Indexacute (CFI-a), and Columbia Suicide Severity Rating Scale's administration, to provide additional information on adverse events of special interest (AESI), and to provide new guidelines for rescreening subjects.
19 December 2017	1) To add an additional blood draw in an optional substudy to characterize the T-cell response to study drug as a possible mechanism of druginduced hepatic enzyme elevation. This substudy was conducted in a limited set of subjects who experienced hepatic enzyme elevations. 2) To update and clarify 2 exclusion criteria, 3) To broaden criteria for medical professional permitted to perform skin examination, 4) To add the definition of the primary estimand to reflect the recent draft International Conference on Harmonisation (ICH) E9 addendum and the feedback received from health authorities, and 5) Other minor clarifications.
25 May 2018	1) Cessation of screening, randomization, and dosing, 2) JNJ 54861911 changed to atabecestat, and 3) other minor editorial updates.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

17 May 2018	Due to study termination only about 1/3 of the subjects had PACC data at 6 months. As a result, some imbalances are likely among the remainder who did have post-baseline cognitive data, as small numbers of subjects in treatment arms increase the risk for imbalanced effects. In addition, factors to ensure balanced cognitive abilities were not stratified because larger enrollment numbers were assumed. Another important limitation of the study is the shift in the enrollment population over time, resulting in earlier subjects being more likely to contribute post-baseline data than later ones. Earlier subjects represented different countries, languages and test translations than the total population.	-

Notes:

Limitations and caveats

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

Early termination of study/program due to a change in benefit-risk profile for individuals with early sporadic AD because of elevations in liver enzymes in participants receiving JNJ-54861911.

Notes: