



Clinical trial results:

A Phase 2a Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multi-center Study Investigating the Safety and Tolerability of JNJ-54861911 in Subjects in the Early (Predementia) Alzheimer's Disease Spectrum

Summary

EudraCT number	2014-002159-24
Trial protocol	BE SE ES NL DE
Global end of trial date	11 June 2016

Results information

Result version number	v1 (current)
This version publication date	06 December 2017
First version publication date	06 December 2017

Trial information

Trial identification

Sponsor protocol code	54861911ALZ2002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02260674
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV (JCI)
Sponsor organisation address	Turnhoutseweg 30, B2340 Beerse, Belgium,
Public contact	Janssen-Cilag International NV, Clinical Registry Group, ClinicalTrialsEU@its.jnj.com
Scientific contact	Janssen-Cilag International NV, Clinical Registry Group, 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	11 June 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to investigate the longer-term safety and tolerability of JNJ-54861911 during 6 months of treatment in subjects in the early (predementia) Alzheimer's Disease (AD) spectrum.

Protection of trial subjects:

The safety assessments included monitoring of adverse events (AEs), changes in clinical laboratory test values (hematology, serum chemistry, alpha 1-acid glycoprotein, coagulation, urinalysis and hormones), vital sign measurements, physical and neurological examination results, ophthalmologic examinations, dermatological examinations and Electrocardiogram (ECG) at defined timepoints from screening phase through study completion.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 February 2016
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	Belgium: 15
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Spain: 46
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Sweden: 14
Worldwide total number of subjects	114
EEA total number of subjects	114

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)	25
From 65 to 84 years	89
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted from 12 February 2016 to 11 June 2016 at 21 sites in 6 countries.

Pre-assignment

Screening details:

A total of 114 subjects were enrolled in this study, including 27 subjects who participated previously in study 54861911ALZ1005 (roll-over subjects). Subjects who did not previously participate were randomly assigned to 1 of the 3 treatment groups and subjects who previously participated were continued on the same blinded treatment.

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received matching placebo as 2 oral tablets once daily for at least 2 months. After amendment 4, the dose was lowered to 1 oral tablet once daily up to Month 6 to match JNJ-54861911 5 or 25 milligrams per day (mg/day) dose groups.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo as 1 or 2 oral tablets once daily matching to dose of assigned dose groups.

Arm title	JNJ-54861911 10 mg
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Arm description:

Subjects received JNJ-54861911 10 mg as (2*5 mg) oral tablets once daily for at least 2 months. After amendment 4, the dose was lowered to 5 mg (1 tablet) once daily up to Month 6.

Arm type	Experimental
Investigational medicinal product name	JNJ-54861911
Investigational medicinal product code	
Other name	JNJ-54861911-AAA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received JNJ-54861911 10 mg as (2*5 mg) oral tablets once daily.

Arm title	JNJ-54861911 50 mg
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Arm description:

Subjects received JNJ-54861911 50 mg as (2*25 mg) oral tablets once daily for at least 2 months. After amendment 4, the dose was lowered to 25 mg (1 tablet) once daily up to Month 6.

Arm type	Experimental
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Investigational medicinal product name	JNJ-54861911
Investigational medicinal product code	
Other name	JNJ-54861911-AAA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received JNJ-54861911 50 mg as (2*25 mg) oral tablets once daily.

Number of subjects in period 1	Placebo	JNJ-54861911 10 mg	JNJ-54861911 50 mg
Started	39	37	38
Completed	37	34	28
Not completed	2	3	10
Adverse event, serious fatal	-	1	-
Physician decision	1	-	1
Consent withdrawn by subject	-	1	2
Adverse event, non-fatal	1	1	6
Noncompliance with study drug	-	-	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo as 2 oral tablets once daily for at least 2 months. After amendment 4, the dose was lowered to 1 oral tablet once daily up to Month 6 to match JNJ-54861911 5 or 25 milligrams per day (mg/day) dose groups.	
Reporting group title	JNJ-54861911 10 mg
Reporting group description:	
Subjects received JNJ-54861911 10 mg as (2*5 mg) oral tablets once daily for at least 2 months. After amendment 4, the dose was lowered to 5 mg (1 tablet) once daily up to Month 6.	
Reporting group title	JNJ-54861911 50 mg
Reporting group description:	
Subjects received JNJ-54861911 50 mg as (2*25 mg) oral tablets once daily for at least 2 months. After amendment 4, the dose was lowered to 25 mg (1 tablet) once daily up to Month 6.	

Reporting group values	Placebo	JNJ-54861911 10 mg	JNJ-54861911 50 mg
Number of subjects	39	37	38
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	6	12
From 65 to 84 years	32	31	26
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	70.3	70.9	68.1
standard deviation	± 5.38	± 6.58	± 8.55
Title for Gender Units: subjects			
Female	23	19	18
Male	16	18	20

Reporting group values	Total		
Number of subjects	114		
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	25		
From 65 to 84 years	89		
85 years and over	0		
Title for AgeContinuous Units: years			
arithmetic mean			
standard deviation	-		

Title for Gender			
Units: subjects			
Female	60		
Male	54		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Subjects received matching placebo as 2 oral tablets once daily for at least 2 months. After amendment 4, the dose was lowered to 1 oral tablet once daily up to Month 6 to match JNJ-54861911 5 or 25 milligrams per day (mg/day) dose groups.	
Reporting group title	JNJ-54861911 10 mg
Reporting group description: Subjects received JNJ-54861911 10 mg as (2*5 mg) oral tablets once daily for at least 2 months. After amendment 4, the dose was lowered to 5 mg (1 tablet) once daily up to Month 6.	
Reporting group title	JNJ-54861911 50 mg
Reporting group description: Subjects received JNJ-54861911 50 mg as (2*25 mg) oral tablets once daily for at least 2 months. After amendment 4, the dose was lowered to 25 mg (1 tablet) once daily up to Month 6.	

Primary: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) ^[1]
End point description: An Adverse Event (AE) was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. Treatment-emergent were events between administration of study drug and up to Month 6 that were absent before treatment or that worsened relative to pretreatment state. subjects who were randomized, received at least 1 dose of double-blind study drug, and contributed safety data after the start of study treatment.	
End point type	Primary
End point timeframe: up to 6 months (Treatment Period)	
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: Only descriptive statistics was performed and no inferential statistical analyses was performed for this endpoint.	

End point values	Placebo	JNJ-54861911 10 mg	JNJ-54861911 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	37	38	
Units: Subjects	27	23	31	

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of JNJ-54861911

End point title	Plasma Concentration of JNJ-54861911 ^[2]
End point description: Plasma concentration of JNJ- 54861911 were assessed. Here, 'Number of subjects analysed' represents the number of subjects evaluable for this outcome measure and 'n' represents the number of subjects	

evaluable for the specific category. PK populations included all subjects who were evaluable for PK analysis.

End point type	Secondary
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End point timeframe:

Days 28, 56, 84, 112, 140 and 168

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data was planned to be reported for the specified arms only.

End point values	JNJ-54861911 10 mg	JNJ-54861911 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	38		
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Day 28 (n = 36,38)	38.39 (± 36.532)	214.38 (± 238.259)		
Day 56 (n = 36,36)	31.76 (± 21.745)	179.05 (± 182.705)		
Day 84 (n = 35,32)	25.90 (± 13.838)	175.20 (± 159.107)		
Day 112 (n = 35,30)	25.53 (± 15.513)	124.57 (± 102.414)		
Day 140 (n = 32,30)	22.01 (± 11.031)	114.00 (± 85.782)		
Day 168 (n = 34,28)	19.65 (± 11.355)	114.94 (± 96.962)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cerebrospinal Fluid (CSF) Concentration of JNJ-54861911

End point title	Cerebrospinal Fluid (CSF) Concentration of JNJ-54861911 ^[3]
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End point description:

Cerebrospinal Fluid (CSF) concentration of JNJ-54861911 were assessed. Here, 'Number of subjects analysed' represents the number of subjects evaluable for this outcome measure. PK populations included all subjects who were evaluable for PK analysis.

End point type	Secondary
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End point timeframe:

Day 168

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data was planned to be reported for the specified arms only.

End point values	JNJ-54861911 10 mg	JNJ-54861911 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	22		
Units: ng/mL				
arithmetic mean (standard deviation)	1.88 (± 1.156)	10.50 (± 8.124)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in CSF Amyloid-Beta (A-Beta) Fragments at Day 168

End point title	Percent Change From Baseline in CSF Amyloid-Beta (A-Beta) Fragments at Day 168
End point description: Percent change from baseline in CSF A-beta species (A beta 1-37, A beta 1-38, A beta 1-40 and A beta 1-42) were summarized. subjects who were randomized, received at least 1 dose of double-blind study drug, and contributed safety data after the start of study treatment. Here 'n' represents the number of subjects evaluable for specific category.	
End point type	Secondary
End point timeframe: Day 168	

End point values	Placebo	JNJ-54861911 10 mg	JNJ-54861911 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39 ^[4]	37 ^[5]	38 ^[6]	
Units: percent change				
arithmetic mean (standard deviation)				
Amyloid Beta 1-37 (n = 27,30)	-1.37 (± 14.558)	-47.09 (± 19.240)	-81.41 (± 11.400)	
Amyloid Beta 1-38 (n = 27,29)	0.19 (± 14.345)	-44.92 (± 18.574)	-80.07 (± 12.239)	
Amyloid Beta 1-40 (n = 27,30)	-1.48 (± 15.972)	-48.93 (± 15.608)	-82.28 (± 10.087)	
Amyloid Beta 1-42 (n = 27,30)	-5.94 (± 18.985)	-43.94 (± 16.894)	-76.86 (± 10.546)	

Notes:

[4] - Safety analysis population

[5] - Safety analysis population

[6] - Safety analysis population

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in CSF Soluble Amyloid Precursor Protein (sAPP) Fragments at Day 168

End point title	Percent Change From Baseline in CSF Soluble Amyloid Precursor Protein (sAPP) Fragments at Day 168
End point description: Percent change from baseline in CSF sAPP (sAPP alpha, sAPP beta) fragments were summarized. subjects who were randomized, received at least 1 dose of double-blind study drug, and contributed safety data after the start of study treatment. Here 'n' represents the number of subjects evaluable for specific category.	
End point type	Secondary
End point timeframe: Day 168	

End point values	Placebo	JNJ-54861911 10 mg	JNJ-54861911 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39 ^[7]	37 ^[8]	38 ^[9]	
Units: percent change				
arithmetic mean (standard deviation)				
sAPPa (n = 27,30)	-3.30 (± 14.642)	61.76 (± 19.489)	115.35 (± 43.132)	
sAPPβ (n = 27,30)	-3.34 (± 15.005)	-49.76 (± 15.941)	-81.00 (± 11.440)	

Notes:

[7] - Safety analysis population

[8] - Safety analysis population

[9] - Safety analysis population

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Amyloid-Beta Fragment (1-40) Levels at Baseline and day 168

End point title	Plasma Amyloid-Beta Fragment (1-40) Levels at Baseline and day 168
End point description: Plasma A beta (1-40) levels were summarized. Subjects who were randomized, received at least 1 dose of double-blind study drug, and contributed safety data after the start of study treatment. Here 'N' represents the number of subjects evaluable for specific outcome measure.	
End point type	Secondary
End point timeframe: Baseline, Day 168	

End point values	Placebo	JNJ-54861911 10 mg	JNJ-54861911 50 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35	34	28	
Units: nanogram per liter (ng/L)				
arithmetic mean (standard deviation)				
Baseline	165.98 (± 49.744)	162.88 (± 60.785)	172.18 (± 41.431)	

Day 168	170.33 (\pm 34.141)	56.43 (\pm 20.604)	24.56 (\pm 9.344)	
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Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening up to follow-up (approximately 10 months)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects received matching placebo as 2 oral tablets once daily for at least 2 months. After amendment 4, the dose was lowered to 1 oral tablet once daily up to Month 6 to match JNJ-54861911 5 or 25 milligrams per day (mg/day) dose groups.

Reporting group title	JNJ-54861911 50 mg
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Reporting group description:

Subjects received JNJ-54861911 50 mg as (2*25 mg) oral tablets once daily for at least 2 months. After amendment 4, the dose was lowered to 25 mg (1 tablet) once daily up to Month 6.

Reporting group title	JNJ-54861911 10 mg
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Reporting group description:

Subjects received JNJ-54861911 10 mg as (2*5 mg) oral tablets once daily for at least 2 months. After amendment 4, the dose was lowered to 5 mg (1 tablet) once daily up to Month 6.

Serious adverse events	Placebo	JNJ-54861911 50 mg	JNJ-54861911 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 39 (10.26%)	8 / 38 (21.05%)	2 / 37 (5.41%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Investigations			
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	0 / 39 (0.00%)	1 / 38 (2.63%)	0 / 37 (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
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 39 (0.00%)	1 / 38 (2.63%)	0 / 37 (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
Transaminases Increased			

subjects affected / exposed	0 / 39 (0.00%)	2 / 38 (5.26%)	0 / 37 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma			
subjects affected / exposed	0 / 39 (0.00%)	0 / 38 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Squamous Cell Carcinoma of Head and Neck			
subjects affected / exposed	1 / 39 (2.56%)	0 / 38 (0.00%)	0 / 37 (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
Injury, poisoning and procedural complications			
Femoral Neck Fracture			
subjects affected / exposed	0 / 39 (0.00%)	1 / 38 (2.63%)	0 / 37 (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
Head Injury			
subjects affected / exposed	1 / 39 (2.56%)	0 / 38 (0.00%)	0 / 37 (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
Joint Dislocation			
subjects affected / exposed	0 / 39 (0.00%)	1 / 38 (2.63%)	0 / 37 (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
Vascular disorders			
Temporal Arteritis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 38 (2.63%)	0 / 37 (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
Cardiac disorders			
Bradycardia			

subjects affected / exposed	0 / 39 (0.00%)	0 / 38 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Tamponade			
subjects affected / exposed	1 / 39 (2.56%)	0 / 38 (0.00%)	0 / 37 (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			
Syncope			
subjects affected / exposed	1 / 39 (2.56%)	0 / 38 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Inguinal Hernia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 38 (2.63%)	0 / 37 (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
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 38 (2.63%)	0 / 37 (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
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 38 (0.00%)	0 / 37 (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
Cholelithiasis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 38 (0.00%)	0 / 37 (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
Skin and subcutaneous tissue disorders			
Toxic Skin Eruption			

subjects affected / exposed	0 / 39 (0.00%)	1 / 38 (2.63%)	0 / 37 (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
Renal and urinary disorders			
Bladder Neck Sclerosis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 38 (2.63%)	0 / 37 (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
Haematuria			
subjects affected / exposed	1 / 39 (2.56%)	0 / 38 (0.00%)	0 / 37 (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			
Urinary Tract Infection			
subjects affected / exposed	1 / 39 (2.56%)	0 / 38 (0.00%)	0 / 37 (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 50 mg	JNJ-54861911 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 39 (48.72%)	24 / 38 (63.16%)	15 / 37 (40.54%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 39 (7.69%)	1 / 38 (2.63%)	2 / 37 (5.41%)
occurrences (all)	3	1	2
General disorders and administration site conditions			
Influenza Like Illness			
subjects affected / exposed	1 / 39 (2.56%)	2 / 38 (5.26%)	0 / 37 (0.00%)
occurrences (all)	1	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 39 (0.00%)	3 / 38 (7.89%)	2 / 37 (5.41%)
occurrences (all)	0	3	2

Psychiatric disorders Mood Altered subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	2 / 38 (5.26%) 2	1 / 37 (2.70%) 1
Investigations Alanine Aminotransferase Increased subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 38 (0.00%) 0	2 / 37 (5.41%) 2
Transaminases Increased subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 38 (2.63%) 1	2 / 37 (5.41%) 2
Vitamin B12 Decreased subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	0 / 38 (0.00%) 0	0 / 37 (0.00%) 0
Injury, poisoning and procedural complications Procedural Pain subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	3 / 38 (7.89%) 3	0 / 37 (0.00%) 0
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 38 (2.63%) 2	2 / 37 (5.41%) 2
Headache subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 6	2 / 38 (5.26%) 2	2 / 37 (5.41%) 3
Syncope subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3	0 / 38 (0.00%) 0	0 / 37 (0.00%) 0
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	2 / 38 (5.26%) 2	0 / 37 (0.00%) 0
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	2 / 38 (5.26%) 2	1 / 37 (2.70%) 1
Eye disorders			

Cataract subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	0 / 38 (0.00%) 0	0 / 37 (0.00%) 0
Gastrointestinal disorders			
Abdominal Pain subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	2 / 38 (5.26%) 2	0 / 37 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 3	7 / 38 (18.42%) 7	3 / 37 (8.11%) 4
Gastrooesophageal Reflux Disease subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	2 / 38 (5.26%) 2	0 / 37 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 4	0 / 38 (0.00%) 0	0 / 37 (0.00%) 0
Skin and subcutaneous tissue disorders			
Actinic Keratosis subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	0 / 38 (0.00%) 0	0 / 37 (0.00%) 0
Eczema subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	3 / 38 (7.89%) 4	0 / 37 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	2 / 38 (5.26%) 2	2 / 37 (5.41%) 2
Urticaria subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	2 / 38 (5.26%) 2	0 / 37 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Back Pain subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 3	2 / 38 (5.26%) 2	2 / 37 (5.41%) 2
Tendonitis subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	2 / 38 (5.26%) 2	1 / 37 (2.70%) 1

Infections and infestations Influenza subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	2 / 38 (5.26%) 3	0 / 37 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 5	3 / 38 (7.89%) 3	3 / 37 (8.11%) 3
Urinary Tract Infection subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 4	0 / 38 (0.00%) 0	1 / 37 (2.70%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2015	Amendment included the following changes: Clarification on the ophthalmologic and Optical Coherence Tomography (OCT) examinations described; Statement describing the audiotaping and central review of the Clinical Dementia Rating Scale (CDR); The replacement of multiple Ribonucleic Acid (RNA) samples during treatment by a single plasma pharmacodynamic (PD) sample during screening in order to correlate the screening Cerebrospinal Fluid (CSF) biomarker profile with the plasma profile; Implementation of comments/remarks received by the different Health Authorities and Ethics Committees during the initial review of the protocol; Adjustment of the Electrocardiogram (ECG) collections to triplicate recordings at all time points and a shift from pre dose to post dose assessments post Day 1 based on the preliminary outcome of the tQT study (54861911ALZ1007); Update in concomitant medication based on in vitro transporter Drug-Drug Interaction (DDI) studies as well as preliminary data of the clinical DDI studies performed; For subjects rolling over from study 54861911ALZ1005: a new baseline Magnetic Resonance Imaging (MRI) scan might have been required (not for eligibility but for on treatment comparisons) in case changes occurred between studies to the technical set up of the MRI for example (e.g.), change of scanner; Inclusion of roll over subjects from study 54861911ALZ1005, aged 60 to 64 years inclusive, who were asymptomatic at risk for Alzheimer's dementia were allowed.
06 March 2015	Amendment included changes to allow the use of moderate and strong cytochrome P450 3A4 (CYP3A4) inhibitors based on the read out of 2 clinical DDI studies (54861911ALZ1009 and 54861911ALZ1010) with an instruction to investigators to use these inhibitors with care. This update was implemented based on 2 clinical DDI studies (54861911ALZ1009 and 54861911ALZ1010), which evaluated the interaction potential of JNJ-54861911 when co-administered with CYP3A4 inhibitors.
08 February 2016	A data review committee (DRC) evaluated the safety data during the course of the study. Based upon the observation of a possible safety signal, instructions regarding a reduction in dosage (from 50 milligrams {mg} to 25 mg and from 10 mg to 5 mg), an increase in the frequency of safety monitoring (additional safety monitoring for liver function at Months 4 and 5), and additional guidance on rules of discontinuation of treatment were provided, implemented urgently with a note to file (28 January 2016), followed by the fourth amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

As a result of an urgent safety measure, the doses of both active arms were reduced by 50 percent (%). Additionally, the groups with a reduction of the dose during study have variable duration of treatment for initial and lowered dose, respectively.

Notes: