



Clinical trial results:

A Blinded Long-term Extension Study to Evaluate the Safety and Efficacy of Pioglitazone (AD-4833 Sustained Release 0.8 mg Daily) to Slow the Progression of Cognitive Decline in Subjects Who Have Completed the AD-4833/TOMM40_301 Study With Diagnosis of Mild Cognitive Impairment Due to Alzheimer Disease

Summary

EudraCT number	2013-004984-30
Trial protocol	GB
Global end of trial date	08 May 2018

Results information

Result version number	v1 (current)
This version publication date	24 May 2019
First version publication date	24 May 2019

Trial information

Trial identification

Sponsor protocol code	AD-4833/TOMM40_303
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02284906
WHO universal trial number (UTN)	U1111-1154-9637

Notes:

Sponsors

Sponsor organisation name	Takeda Development Center Americas, Inc.
Sponsor organisation address	One Takeda Parkway Deerfield, Deerfield, IL, United States, 60015
Public contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.com
Scientific contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.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	08 May 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to evaluate the effect of pioglitazone at 24 months compared with placebo on cognitive decline in high-risk participants who have completed the AD-4833/TOMM40_301 study [NCT01931566] with an adjudicated diagnosis of mild cognitive impairment (MCI) due to Alzheimer's Disease (AD).

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 February 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	United States: 28
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Australia: 7
Worldwide total number of subjects	40
EEA total number of subjects	5

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)	0
From 65 to 84 years	40

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 3 investigative sites in Australia, United Kingdom and United States from 12 Feb 2015 to 08 May 2018.

Pre-assignment

Screening details:

Participants who have completed the pivotal AD-4833/TOMM40_301 (NCT01931566) study with an adjudicated diagnosis of mild cognitive impairment (MCI) due to Alzheimer's Disease (AD) were enrolled to pioglitazone (0.8 mg sustained release tablet) or placebo.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Low Risk Placebo

Arm description:

Pioglitazone placebo-matching tablets, orally, once daily, for 10 months to participants assigned to low risk group for developing MCI- AD within the next five years in previous study (AD-4833/TOMM40_301).

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:

Pioglitazone placebo-matching tablets

Arm title	High Risk Placebo
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Arm description:

Pioglitazone placebo-matching tablets, orally, once daily, for minimum of 3 years to participants assigned to high risk group for developing MCI- AD within the next five years in previous study (AD-4833/TOMM40_301).

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:

Pioglitazone placebo-matching tablets

Arm title	High Risk Pioglitazone
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Arm description:

Pioglitazone 0.8 mg tablets, orally, once daily for 3 years to participants assigned to high risk group for developing MCI- AD within the next five years in previous study (AD-4833/TOMM40_301).

Arm type	Experimental
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Investigational medicinal product name	Pioglitazone
Investigational medicinal product code	
Other name	AD-4833
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pioglitazone tablets

Number of subjects in period 1	Low Risk Placebo	High Risk Placebo	High Risk Pioglitazone
Started	3	18	19
Completed	0	0	0
Not completed	3	18	19
Pretreatment Event/Adverse Event	-	1	-
Major Protocol Deviation	-	1	-
Study Termination	-	11	14
Voluntary Withdrawal	2	4	5
Reason not Specified	1	1	-

Baseline characteristics

Reporting groups

Reporting group title	Low Risk Placebo
Reporting group description: Pioglitazone placebo-matching tablets, orally, once daily, for 10 months to participants assigned to low risk group for developing MCI- AD within the next five years in previous study (AD-4833/TOMM40_301).	
Reporting group title	High Risk Placebo
Reporting group description: Pioglitazone placebo-matching tablets, orally, once daily, for minimum of 3 years to participants assigned to high risk group for developing MCI- AD within the next five years in previous study (AD-4833/TOMM40_301).	
Reporting group title	High Risk Pioglitazone
Reporting group description: Pioglitazone 0.8 mg tablets, orally, once daily for 3 years to participants assigned to high risk group for developing MCI- AD within the next five years in previous study (AD-4833/TOMM40_301).	

Reporting group values	Low Risk Placebo	High Risk Placebo	High Risk Pioglitazone
Number of subjects	3	18	19
Age categorical			
Units: Subjects			
From 65-84 years	3	18	19
Age Continuous			
Units: years			
arithmetic mean	74.7	78.9	78.1
standard deviation	± 4.73	± 3.98	± 4.42
Sex: Female, Male			
Units: Subjects			
Female	1	5	10
Male	2	13	9
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	1	1	1
Not Hispanic or Latino	2	17	18
Race/Ethnicity, Customized			
Units: Subjects			
Black or African American	0	0	1
White	3	18	18
Race/Ethnicity, Customized			
Units: Subjects			
Non-Hispanic/Latino Caucasian	2	17	17
Hispanic/Latino and/or non-Caucasian	1	1	2
Smoking Classification			
Units: Subjects			
Participant Has Never Smoked	2	7	9
Participant is an Ex-smoker	1	11	10
Alcohol Classification			
Units: Subjects			
Participant Has Never Drunk	1	3	3

Participant is a Current Drinker	2	15	15
Participant is an Ex-drinker	0	0	1
Primary Language Units: Subjects			
English	2	16	19
Other	1	2	0
Ability to Communicate in Primary Language Units: Subjects			
Not At All	0	1	0
Very Well	3	17	19
Does Participant Speak More Than Two Languages Units: Subjects			
Yes, Speaks	0	1	0
No, Does not Speak	3	17	19
Region of Enrollment Units: Subjects			
United States	2	11	15
United Kingdom	1	2	2
Australia	0	5	2
Diabetic Status Units: Subjects			
Diabetic	0	3	3
Non-Diabetic	3	15	16
Baseline Statin Use Units: Subjects			
Yes, Statin was used	1	9	8
No, Statin was not used	2	9	11
Years Lived in Country/Region for 10 Years or More Units: Subjects			
Lived >10 years	3	18	19
If Participant Speaks Second Language, Ability to Very Well Communicate in Second Language Units: Subjects			
Yes	0	1	0
No	3	17	19
Height Units: cm			
arithmetic mean	169.7	168.7	166.8
standard deviation	± 4.16	± 10.85	± 11.73
Weight Units: kg			
arithmetic mean	78.20	76.00	72.11
standard deviation	± 6.053	± 13.719	± 15.685
Body Mass Index (BMI)			
BMI=Weight/Height^2. Both weight and height measurements were from extension study baseline, which was conducted at the End of Study visit for the pivotal AD-4833/TOMM40_301 study.			
Units: kg/m^2			
arithmetic mean	27.27	26.49	25.68
standard deviation	± 3.412	± 2.769	± 3.653

Years of Education Units: years arithmetic mean standard deviation	15.0 ± 3.61	14.8 ± 3.59	14.9 ± 3.67
Reporting group values	Total		
Number of subjects	40		
Age categorical Units: Subjects			
From 65-84 years	40		
Age Continuous Units: years arithmetic mean standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	16		
Male	24		
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	3		
Not Hispanic or Latino	37		
Race/Ethnicity, Customized Units: Subjects			
Black or African American	1		
White	39		
Race/Ethnicity, Customized Units: Subjects			
Non-Hispanic/Latino Caucasian	36		
Hispanic/Latino and/or non-Caucasian	4		
Smoking Classification Units: Subjects			
Participant Has Never Smoked	18		
Participant is an Ex-smoker	22		
Alcohol Classification Units: Subjects			
Participant Has Never Drunk	7		
Participant is a Current Drinker	32		
Participant is an Ex-drinker	1		
Primary Language Units: Subjects			
English	37		
Other	3		
Ability to Communicate in Primary Language Units: Subjects			
Not At All	1		
Very Well	39		
Does Participant Speak More Than Two Languages Units: Subjects			

Yes, Speaks	1		
No, Does not Speak	39		
Region of Enrollment			
Units: Subjects			
United States	28		
United Kingdom	5		
Australia	7		
Diabetic Status			
Units: Subjects			
Diabetic	6		
Non-Diabetic	34		
Baseline Statin Use			
Units: Subjects			
Yes, Statin was used	18		
No, Statin was not used	22		
Years Lived in Country/Region for 10 Years or More			
Units: Subjects			
Lived >10 years	40		
If Participant Speaks Second Language, Ability to Very Well Communicate in Second Language			
Units: Subjects			
Yes	1		
No	39		
Height			
Units: cm			
arithmetic mean			
standard deviation	-		
Weight			
Units: kg			
arithmetic mean			
standard deviation	-		
Body Mass Index (BMI)			
BMI=Weight/Height^2. Both weight and height measurements were from extension study baseline, which was conducted at the End of Study visit for the pivotal AD-4833/TOMM40_301 study.			
Units: kg/m^2			
arithmetic mean			
standard deviation	-		
Years of Education			
Units: years			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Low Risk Placebo
Reporting group description: Pioglitazone placebo-matching tablets, orally, once daily, for 10 months to participants assigned to low risk group for developing MCI- AD within the next five years in previous study (AD-4833/TOMM40_301).	
Reporting group title	High Risk Placebo
Reporting group description: Pioglitazone placebo-matching tablets, orally, once daily, for minimum of 3 years to participants assigned to high risk group for developing MCI- AD within the next five years in previous study (AD-4833/TOMM40_301).	
Reporting group title	High Risk Pioglitazone
Reporting group description: Pioglitazone 0.8 mg tablets, orally, once daily for 3 years to participants assigned to high risk group for developing MCI- AD within the next five years in previous study (AD-4833/TOMM40_301).	

Primary: Change from Extension Study Baseline in Composite Score of a Broad Cognitive Test Battery at Month 24

End point title	Change from Extension Study Baseline in Composite Score of a Broad Cognitive Test Battery at Month 24 ^[1]
End point description: Composite scores were derived from the test battery. Each test in the battery falls into 1 of the following cognitive domains: Episodic Memory, Executive Function, Language, Attention and Visuospatial. Only the domains of episodic memory, executive function, language, and attention were used for the calculation of composite score (i.e., Clock Drawing, Brief Visuospatial Memory Test [BVM]-Copy, and the Multilingual Naming Test [MINT], which do not allow generation of standard z scores, were only used for diagnostic purposes and were excluded from the calculation of the composite score). To form the composite, z-scores were calculated for each test, each z-score for the domain were averaged, and then all relevant domains were averaged to form the composite. As the study was early terminated, there were limited number of enrolled participants and insufficient treatment duration, therefore, efficacy analysis was not performed as planned.	
End point type	Primary
End point timeframe: Baseline and 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: No statistical analysis available.

End point values	Low Risk Placebo	High Risk Placebo	High Risk Pioglitazone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[2]	0 ^[3]	0 ^[4]	
Units: Z score				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[2] - Number of subjects analyzed is 0 as efficacy analysis was not performed.

[3] - Number of subjects analyzed is 0 as efficacy analysis was not performed.

[4] - Number of subjects analyzed is 0 as efficacy analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Diagnosis of Alzheimer's Disease (AD) Dementia

End point title	Time to Diagnosis of Alzheimer's Disease (AD) Dementia
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End point description:

As the study was early terminated, there were limited number of enrolled participants and insufficient treatment duration, therefore, efficacy analysis was not performed as planned.

End point type	Secondary
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End point timeframe:

Day 1 and every 6 months (up to maximum of 36 months)

End point values	Low Risk Placebo	High Risk Placebo	High Risk Pioglitazone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[5]	0 ^[6]	0 ^[7]	
Units: Months				
median (full range (min-max))	(to)	(to)	(to)	

Notes:

[5] - Number of subjects analyzed is 0 as efficacy analysis was not performed.

[6] - Number of subjects analyzed is 0 as efficacy analysis was not performed.

[7] - Number of subjects analyzed is 0 as efficacy analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 30 days after receiving the last dose of study drug (approximately up to 1113 days)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Low Risk Placebo
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Reporting group description:

Pioglitazone placebo-matching tablets, orally, once daily, for 10 months to participants assigned to low risk group for developing MCI- AD within the next five years in previous study (AD-4833/TOMM40_301).

Reporting group title	High Risk Placebo
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Reporting group description:

Pioglitazone placebo-matching tablets, orally, once daily, for minimum of 3 years to participants assigned to high risk group for developing MCI- AD within the next five years in previous study (AD-4833/TOMM40_301).

Reporting group title	High Risk Pioglitazone
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Reporting group description:

Pioglitazone 0.8 mg tablets, orally, once daily for 3 years to participants assigned to high risk group for developing MCI- AD within the next five years in previous study (AD-4833/TOMM40_301).

Serious adverse events	Low Risk Placebo	High Risk Placebo	High Risk Pioglitazone
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	4 / 18 (22.22%)	3 / 19 (15.79%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer metastatic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 18 (5.56%)	0 / 19 (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
Injury, poisoning and procedural complications			
Femur fracture			

subjects affected / exposed	0 / 3 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 18 (5.56%)	0 / 19 (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			
Cardiac failure congestive			
subjects affected / exposed	0 / 3 (0.00%)	1 / 18 (5.56%)	0 / 19 (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
Myocardial infarction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 18 (5.56%)	0 / 19 (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
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 18 (5.56%)	0 / 19 (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
Eye disorders			
Retinal artery occlusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
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 / 3 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
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	0 / 3 (0.00%)	1 / 18 (5.56%)	0 / 19 (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

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

Non-serious adverse events	Low Risk Placebo	High Risk Placebo	High Risk Pioglitazone
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	10 / 18 (55.56%)	12 / 19 (63.16%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 3 (0.00%)	2 / 18 (11.11%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Benign neoplasm of skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Malignant melanoma			
subjects affected / exposed	0 / 3 (0.00%)	1 / 18 (5.56%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	0 / 3 (0.00%)	0 / 18 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Immune system disorders			

Seasonal allergy subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1
Respiratory, thoracic and mediastinal disorders			
Hypoxia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0
Psychiatric disorders			
Depression subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0
Injury, poisoning and procedural complications			
Fall subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 18 (5.56%) 1	2 / 19 (10.53%) 2
Contusion subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0
Skin abrasion subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1
Nervous system disorders			
Cerebral infarction subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1
Dementia Alzheimer's type subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 18 (0.00%) 0	0 / 19 (0.00%) 0
Syncope			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0
Eye disorders Cataract subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 18 (0.00%) 0	2 / 19 (10.53%) 3
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1
Diarrhoea subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 18 (0.00%) 0	0 / 19 (0.00%) 0
Haemorrhoids subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1
Large intestine polyp subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1
Pancreatic cyst subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0
Hepatobiliary disorders Hepatic mass subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1
Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1
Skin lesion subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 18 (0.00%) 0	1 / 19 (5.26%) 2

Urinary retention subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 18 (0.00%) 0	2 / 19 (10.53%) 2
Back pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0
Bursitis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1
Rotator cuff syndrome subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 18 (5.56%) 1	0 / 19 (0.00%) 0
Infections and infestations			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 18 (11.11%) 2	4 / 19 (21.05%) 4
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 18 (11.11%) 4	1 / 19 (5.26%) 1
Metabolism and nutrition disorders			
Hyponatraemia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 18 (0.00%) 0	1 / 19 (5.26%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2015	The following changes were made as per Amendment 1: The Health Care RU instrument was replaced by the Alzheimer's Disease Cooperative Study – Resource Use Inventory (ADCS-RUI) within the protocol. Additional assessments for the project partners were added including the European Quality of Life Scale (Euro-QoL EQ-5D) and the Work Productivity and Activity Impairment Questionnaire: Mood and Mental State, Caregiver Version (WPAI:MM-CG). The ADCS Alzheimer's Disease Cooperative Study Activities of Daily Living – Preventive instrument/Mild Cognitive Impairment (ADL-PI/MCI) was updated to the ADCS Alzheimer's Disease Cooperative Study Activities of Daily Living – Mild Cognitive Impairment (ADL-MCI) version. The adjudication decision option of MCI due to Alzheimer's Disease (AD) was removed. The 2 options of meets AD dementia or does not meet criteria for AD dementia more appropriately support the endpoint for this study MRI were added as a requirement for adjudication. The 36-Item Short Form Health Survey (SF-36) was removed from the study as all necessary information related to health-related quality of life (HRQoL) was captured from the revised assessment schedule of the European Quality of Life 5-Dimension (EQ-5D).
29 July 2015	The following changes were made as per Amendment 2: Due to the change in the study design for the AD-833/TOMM40_301 study, that impacted the effect size, the potential number of subjects anticipated to rollover into the 303 study has been reduced from approximately 316 to 149. Changed the scope of site participation in the extension study, AD-4833/TOMM40_303. Since not all sites participated in the extension study, not all participants with an adjudicated diagnosis of mild cognitive impairment (MCI) due to AD in the 301 study were able to participate in 303. Russia and Italy were removed from AD-4833/TOMM40_301 and therefore, were also removed from this extension study. Exclusion criterion #8 was updated to be consistent with the AD-4833/TOMM40_301 study to clarify allowable repeat testing for hematuria. Criterion #12 was re-worded to be consistent with the AD-4833/TOMM40_301 study, where the correction of removing "any maculopathy" was made and approved in Amendment 1, then inadvertently reinserted in the body of the Amendment 2. Updated excluded medications table. Updated the assessor expectations for the Alzheimer's Disease Cooperative Study – Resource Use Inventory (ADCS-RUI) assessment.
19 January 2016	The following changes were made as per Amendment 3: HbA1c >8% as a criteria for exclusion was removed because this assessment was collected at Baseline, it was no longer considered an important eligibility criterion for this study. Exclusion criterion #8 was modified to allow the eligibility decision to be based on the laboratory results available prior to the AD-4833/TOMM40_301 EOS/303 Baseline visit to confirm/ensure eligibility for this extension study. Removed the adjudication process for confirmation of the diagnosis of dementia and added CDR Global score of ≥ 1.0 as a minimum standard for consistency in diagnosis of AD dementia. Removed magnetic resonance imaging (MRI) and computerized axial tomography (CT) scan (for participants with contraindication to MRI) at the Unscheduled Visit to support the possible dementia diagnosis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported