Clinical trial results:
A 36-Week Safety Extension Study of Oral ELND005 for Treatment of Agitation and Aggression in Patients With Moderate to Severe Alzheimer's Disease

Summary

EudraCT number	2012-005524-15
Trial protocol	GB ES
Global end of trial date	18 August 2015

Results information

Result version number	v1 (current)
This version publication date	24 June 2016
First version publication date	24 June 2016

Trial information

Trial identification

Sponsor protocol code	ELND005-AG251

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01766336
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Transition Therapeutics Ireland Limited
Sponsor organisation address	Arthur Cox Building, Earlsfort Centre, Earlsfort Terrace, Dublin, Ireland, Dublin 2
Public contact	Aleksandra Pastrak, MD, PhD, VP of Clinical Development and Medical Officer, Transition Therapeutics Ireland Limited, +1 416 263 1227, apastrak@transitiontherapeutics.com
Scientific contact	Aleksandra Pastrak, MD, PhD, VP of Clinical Development and Medical Officer, Transition Therapeutics Ireland Limited, +1 416 263 1227, apastrak@transitiontherapeutics.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 August 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of ELND005 treatment with up to 24 weeks exposure, in Moderate to Severe Alzheimer's Disease patients with agitation and aggression.
To evaluate the effects and persistence of effects of ELND005 on agitation and aggression and other assessments including neuropsychiatric symptoms, cognitive status, patient's dependence status and caregiver distress.

Protection of trial subjects:

400 subjects were planned. This study was conducted according to ICH guidelines concerning Good Clinical Practice.

Background therapy:

During the Treatment Period, the doses of concomitant antidepressants, mood stabilizers, permitted doses of specified antipsychotics, cholinesterase inhibitors, memantine, and other permitted medications for the treatment of non-excluded medical conditions were maintained constant.

Evidence for comparator: -

Actual start date of recruitment	19 February 2013
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	Spain: 19
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	United States: 257
Worldwide total number of subjects	296
EEA total number of subjects	24

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	27
From 65 to 84 years	231
85 years and over	38

Subject disposition

Recruitment

Recruitment details:

Patients enrolled from February 2013 to May 2015.

Pre-assignment

Screening details:

Patients that completed Study AG201 and who were willing and eligible to continue into AG251 open-label safety extension study.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Blinding from study AG201 was maintained in this extension study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/ELND005

Arm description:

ELND005 250 mg

Arm type	Experimental
Investigational medicinal product name	ELND005
Investigational medicinal product code	
Other name	Scyllo Inositol
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Group 1- ELND005/ELND005 250 mg Tablet BID (Mock loading dose to maintain blind)
Group 2- 1000 mg BID for 4 weeks followed by 250 mg BID for 32 weeks

Arm title	ELND005/ELND005

Arm description:

ELND005 250 mg

Arm type	Experimental
Investigational medicinal product name	ELND005
Investigational medicinal product code	
Other name	Scyllo Inositol
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Group 1- ELND005/ELND005 250 mg Tablet BID (Mock loading dose to maintain blind)
Group 2- 1000 mg BID for 4 weeks followed by 250 mg BID for 32 weeks

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

Dosage and administration details:

Patients who met eligibility criteria and who received ELND005 during Study AG201 were assigned to Group 1 in Study AG251 and received a mock loading dose of ELND005 (one 250 mg ELND005 tablet and three matching placebo tablets BID for 4 weeks) followed by a Maintenance Dose of 250 mg BID for subsequent 32 weeks.

Number of subjects in period 1	Placebo/ELND005	ELND005/ELND005
Started	146	150
Completed	71	60
Not completed	75	90
Consent withdrawn by subject	15	18
Physician decision	2	4
adverse event, not serious	8	11
death	3	4
Lost to follow-up	3	1
sponsor's decision	43	52
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo/ELND005
Reporting group description: ELND005 250 mg	
Reporting group title	ELND005/ELND005
Reporting group description: ELND005 250 mg	

Reporting group values	Placebo/ELND005	ELND005/ELND005	Total
Number of subjects	146	150	296
Age categorical Units: Subjects			
Adults (18-64 years)	17	10	27
From 65-84 years	110	121	231
85 years and over	19	19	38
Age continuous Units: years			
arithmetic mean	75.8	76.6	
standard deviation	± 8.7	± 7.9	-
Gender categorical Units: Subjects			
Female	81	84	165
Male	65	66	131
Race Units: Subjects			
White	127	138	265
Black	17	10	27
Asian	1	1	2
Other	1	1	2

Subject analysis sets	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description: All patients who were enrolled into the study and received at least one dose of study drug.	

Reporting group values	Safety Analysis Set		
Number of subjects	296		
Age categorical Units: Subjects			
Adults (18-64 years)	27		
From 65-84 years	231		
85 years and over	38		

Age continuous Units: years arithmetic mean standard deviation	 ±		
Gender categorical Units: Subjects			
Female Male	165 131		
Race Units: Subjects			
White Black Asian Other			

End points

End points reporting groups

Reporting group title	Placebo/ELND005
Reporting group description: ELND005 250 mg	
Reporting group title	ELND005/ELND005
Reporting group description: ELND005 250 mg	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description: All patients who were enrolled into the study and received at least one dose of study drug.	

Primary: Change from Baseline to Week 36 in NPI-C A+A Score

End point title	Change from Baseline to Week 36 in NPI-C A+A Score[1]
End point description: Changes from Baseline to Week 36 in Study AG251 (for all patients), and changes from Baseline in Study AG201 to Week 36 of Study AG251 (for patients in Group 1: ELND005/ELND005)	
End point type	Primary
End point timeframe: Up to 36 weeks	

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: Study discontinued prematurely. No Efficacy Analysis performed.

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	296			
Units: NPI-C A+A Score	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All subjects who were enrolled in the study and received at least one dose of study drug were included in safety analyses. Mean duration on study for subjects in the ELND005 group was 153.6 days and for subjects in the placebo group was 167.4 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo/ELND005

Reporting group description:

Patients who met study eligibility criteria and who received placebo during Study AG201 were assigned to Group 2 in Study AG251, and received a loading dose of ELND005 (four 250 mg ELND005 tablets BID for 4 weeks) followed by a Maintenance Dose of 250 mg BID for a subsequent 32 weeks, for a total of up to 36 consecutive weeks of active treatment.

Reporting group title	ELND005/ELND005

Reporting group description:

Patients who met eligibility criteria and who received ELND005 during Study AG201 were assigned to Group 1 in Study AG251 and received a mock loading dose of ELND005 (one 250 mg ELND005 tablet and three matching placebo tablets BID for 4 weeks) followed by a Maintenance Dose of 250 mg BID for a subsequent 32 weeks. Thus, patients in Group 1 might have received up to a total of 48 consecutive weeks of active treatment (12 weeks during Study AG201 and 36 weeks during Study AG251).

Serious adverse events	Placebo/ELND005	ELND005/ELND005	
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 146 (17.81%)	29 / 150 (19.33%)	
number of deaths (all causes)	8	7	
number of deaths resulting from adverse events	8	7	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	1 / 146 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Neoplasm			
subjects affected / exposed	1 / 146 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	0 / 146 (0.00%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Femur Fracture			
subjects affected / exposed	0 / 146 (0.00%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Hip Fracture			
subjects affected / exposed	1 / 146 (0.68%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Femoral Neck Fracture			
subjects affected / exposed	0 / 146 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Laceration			
subjects affected / exposed	0 / 146 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Vascular Pseudoaneurysm			
subjects affected / exposed	0 / 146 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 146 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	1 / 146 (0.68%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	

Cardiac Arrest			
subjects affected / exposed	2 / 146 (1.37%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	2 / 8	0 / 7	
Myocardial Infarction			
subjects affected / exposed	1 / 146 (0.68%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	1 / 8	0 / 7	
Acute Myocardial Infarction			
subjects affected / exposed	0 / 146 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	1 / 7	
Coronary Artery Disease			
subjects affected / exposed	1 / 146 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 146 (0.68%)	3 / 150 (2.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Dementia Alzheimer Type			
subjects affected / exposed	3 / 146 (2.05%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	1 / 8	0 / 7	
Transient Ischaemic Attack			
subjects affected / exposed	1 / 146 (0.68%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Ataxia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Brain Hypoxia			

subjects affected / exposed	0 / 146 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	1 / 7	
Carotid Artery Stenosis			
subjects affected / exposed	1 / 146 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Convulsion			
subjects affected / exposed	0 / 146 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Depressed level of Consciousness			
subjects affected / exposed	0 / 146 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Haemorrhage Intracranial			
subjects affected / exposed	0 / 146 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 146 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	1 / 7	
General Physical Health Deterioration			
subjects affected / exposed	0 / 146 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	1 / 7	
Systemic Inflammatory Response Syndrome			
subjects affected / exposed	0 / 146 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Gastrointestinal disorders			

Gastritis			
subjects affected / exposed	0 / 146 (0.00%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Intestinal Ischaemia			
subjects affected / exposed	1 / 146 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	1 / 146 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	1 / 8	0 / 7	
Bronchospasm			
subjects affected / exposed	1 / 146 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 146 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Pneumonia Aspiration			
subjects affected / exposed	1 / 146 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	1 / 8	0 / 7	
Pulmonary Embolism			
subjects affected / exposed	1 / 146 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Psychiatric disorders			
Mental Status Changes			

subjects affected / exposed	3 / 146 (2.05%)	3 / 150 (2.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	1 / 8	0 / 7	
Agitation			
subjects affected / exposed	3 / 146 (2.05%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Aggression			
subjects affected / exposed	0 / 146 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Behavioural and psychiatric Symptoms of Dementia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Homicidal Ideation			
subjects affected / exposed	1 / 146 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic Disorder			
subjects affected / exposed	1 / 146 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 146 (0.00%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Musculoskeletal Stiffness			
subjects affected / exposed	0 / 146 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Infections and infestations			

Pneumonia			
subjects affected / exposed	1 / 146 (0.68%)	3 / 150 (2.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Bronchitis			
subjects affected / exposed	1 / 146 (0.68%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	1 / 8	1 / 7	
Diverticulitis			
subjects affected / exposed	1 / 146 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Gastroenteritis Viral			
subjects affected / exposed	1 / 146 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Influenza			
subjects affected / exposed	1 / 146 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Metabolism and nutrition disorders			
Failure to Thrive			
subjects affected / exposed	0 / 146 (0.00%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	2 / 7	
Dehydration			
subjects affected / exposed	0 / 146 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	
Hypophagia			
subjects affected / exposed	1 / 146 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 26	0 / 29	
deaths causally related to treatment / all	0 / 8	0 / 7	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo/ELND005	ELND005/ELND005	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 146 (17.81%)	41 / 150 (27.33%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	7 / 146 (4.79%)	20 / 150 (13.33%)	
occurrences (all)	26	41	
Psychiatric disorders			
Agitation			
subjects affected / exposed	14 / 146 (9.59%)	15 / 150 (10.00%)	
occurrences (all)	26	41	
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	7 / 146 (4.79%)	14 / 150 (9.33%)	
occurrences (all)	26	41	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2013	Extended the duration of Study AG251 from 12 weeks to 36 weeks.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported