Clinical trial results:
A Prospective, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Efficacy and Safety Study of Oral ELND005 for Treatment of Agitation and Aggression in Patients With Moderate to Severe Alzheimer's Disease.

Summary

EudraCT number	2012-004299-20
Trial protocol	GB ES
Global end of trial date	20 May 2015

Results information

Result version number	v1 (current)
This version publication date	30 April 2016
First version publication date	30 April 2016

Trial information

Trial identification

Sponsor protocol code	ELND005-AG201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01735630
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, Transition Therapeutics Ireland Limited, 001 416 263 1227, apastrak@transitiontherapeutics.com
Scientific contact	Aleksandra Pastrak,MD, PhD, VP of Clinical Development and Medical Officer, Transition Therapeutics Ireland Limited, 001 416 263 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 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 May 2015
Global end of trial reached?	Yes
Global end of trial date	20 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of ELND005 treatment compared with placebo in reducing the severity of agitation and aggression at 12 weeks;
To evaluate the safety and tolerability of the ELND005 dosing regimen in Moderate to Severe AD patients

Protection of trial subjects:

400 subjects planned
The study was conducted according to /ICH/ guidelines concerning Good Clinical Practice (GCP)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 November 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	9 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	United States: 304
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	350
EEA total number of subjects	29

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)	33
From 65 to 84 years	280
85 years and over	37

Subject disposition

Recruitment

Recruitment details:

Patients recruited between Nov 2012 and Feb 2015.

Pre-assignment

Screening details:

Patients with moderate to severe Alzheimer’s Disease who had clinically significant agitation and aggression.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo matching ELND005

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:

PlaceboTablet - BID for 4 weeks followed by Placebo BID for 8 weeks

Arm title	Test

Arm description:

ELND005 250 mg

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

Dosage and administration details:

250mg Tablet -1000mg BID for 4 weeks followed by 250 mg BID for 8 weeks

Number of subjects in period 1	Placebo	Test
Started	175	175
Completed	157	157
Not completed	18	18
Consent withdrawn by subject	9	7
Physician decision	1	-
Adverse event, non-fatal	7	8
Sponsor desicion	-	2
Sponsor decision	1	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo matching ELND005	
Reporting group title	Test
Reporting group description:	
ELND005 250 mg	

Reporting group values	Placebo	Test	Total
Number of subjects	175	175	350
Age categorical			
Units: Subjects			
Adults (18-64 years)	20	13	33
From 65-84 years	132	142	274
85 years and over	23	20	43
Age continuous			
Units: years			
arithmetic mean	75.9	76.2	
standard deviation	± 8.51	± 7.89	-
Gender categorical			
Units: Subjects			
Female	100	95	195
Male	75	80	155
race			
Units: Subjects			
White	151	155	306
Black	22	17	39
Asian	1	2	3
Other	1	1	2

Subject analysis sets	
Subject analysis set title	modified Intent-to-Treat (mITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects in the safety set (patients that were randomized and received at least one dose of study drug) that had a valid baseline NPI-C A+A assessment and at least one valid post-baseline NPI-C A+A assessment.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who were enrolled in the study and received at least one dose of study drug were included in safety analyses.

Reporting group values	modified Intent-to-Treat (mITT)	Safety Analysis Set	
Number of subjects	334	350	
Age categorical Units: Subjects			
Adults (18-64 years)	30	33	
From 65-84 years	262	274	
85 years and over	42	43	
Age continuous Units: years arithmetic mean standard deviation	 ±	 ±	
Gender categorical Units: Subjects			
Female	187	195	
Male	147	155	
race Units: Subjects			
White	290	306	
Black	39	39	
Asian	3	3	
Other	2	2	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo matching ELND005	
Reporting group title	Test
Reporting group description:	
ELND005 250 mg	
Subject analysis set title	modified Intent-to-Treat (mITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects in the safety set (patients that were randomized and received at least one dose of study drug) that had a valid baseline NPI-C A+A assessment and at least one valid post-baseline NPI-C A+A assessment.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who were enrolled in the study and received at least one dose of study drug were included in safety analyses.	

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

End point title	Change from Baseline in NPI-C A+A Score
End point description:	
Change from Baseline to Week 12 in NPI-C A+A scored between the ELND005 and placebo treatment groups	
End point type	Primary
End point timeframe:	
12 weeks	

End point values	Placebo	Test		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	157		
Units: Change from Baseline Score				
least squares mean (standard error)				
NPI-C A+A	-4.2 (± 0.7)	-4.3 (± 0.7)		

Statistical analyses

Statistical analysis title	Mixed Model Repeated Measured Analyses
Statistical analysis description:	
Mixed Model Repeated Measured Analyses of Change from Baseline in NPI-C A+A Score	
Comparison groups	Placebo v Test

Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8982
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Mean duration on study for subjects in the ELND005 group was 83.6 days and for subjects in the placebo group was 83.8 days.

Adverse event reporting additional description:

All subjects who were enrolled in the study and received at least one dose of study drug were included in safety analyses.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo Safety

Reporting group description:

All subjects who were randomized into the study and received at least one dose of study drug.

Reporting group title	ELND005 250 mg (Safety)

Reporting group description:

All subjects who were randomized into the study and received at least one dose of study drug.

Serious adverse events	Placebo Safety	ELND005 250 mg (Safety)	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 175 (2.86%)	17 / 175 (9.71%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 175 (0.57%)	0 / 175 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	1 / 175 (0.57%)	2 / 175 (1.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetabulum fracture			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 175 (0.57%)	0 / 175 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 175 (0.57%)	0 / 175 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac Failure congestive			
subjects affected / exposed	1 / 175 (0.57%)	0 / 175 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Convulsion			
subjects affected / exposed	0 / 175 (0.00%)	2 / 175 (1.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar infarction			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 175 (0.00%)	2 / 175 (1.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	0 / 175 (0.00%)	2 / 175 (1.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Homocidal ideation			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections Infestations Sepsis			
subjects affected / exposed	0 / 175 (0.00%)	3 / 175 (1.71%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	0 / 175 (0.00%)	3 / 175 (1.71%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 175 (0.00%)	1 / 175 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo Safety	ELND005 250 mg (Safety)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 175 (46.86%)	97 / 175 (55.43%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	9 / 175 (5.14%)	11 / 175 (6.29%)	
occurrences (all)	82	97	
Contusion			
subjects affected / exposed	7 / 175 (4.00%)	1 / 175 (0.57%)	
occurrences (all)	82	97	
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 175 (4.00%)	2 / 175 (1.14%)	
occurrences (all)	82	97	
Lethargy			
subjects affected / exposed	2 / 175 (1.14%)	6 / 175 (3.43%)	
occurrences (all)	82	97	
Somnolence			
subjects affected / exposed	4 / 175 (2.29%)	3 / 175 (1.71%)	
occurrences (all)	82	97	
Headache			
subjects affected / exposed	2 / 175 (1.14%)	4 / 175 (2.29%)	
occurrences (all)	82	97	
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	1 / 175 (0.57%)	4 / 175 (2.29%)	
occurrences (all)	82	97	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	5 / 175 (2.86%)	14 / 175 (8.00%)	
occurrences (all)	82	97	
Vomiting			
subjects affected / exposed	5 / 175 (2.86%)	5 / 175 (2.86%)	
occurrences (all)	82	97	
Constipation			
subjects affected / exposed	2 / 175 (1.14%)	4 / 175 (2.29%)	
occurrences (all)	82	97	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 175 (1.14%)	7 / 175 (4.00%)	
occurrences (all)	82	97	
Psychiatric disorders			
Agitation			
subjects affected / exposed	13 / 175 (7.43%)	14 / 175 (8.00%)	
occurrences (all)	82	97	
Insomnia			
subjects affected / exposed	7 / 175 (4.00%)	5 / 175 (2.86%)	
occurrences (all)	82	97	
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	7 / 175 (4.00%)	12 / 175 (6.86%)	
occurrences (all)	82	97	
Bronchitis			
subjects affected / exposed	5 / 175 (2.86%)	2 / 175 (1.14%)	
occurrences (all)	82	97	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 175 (2.29%)	3 / 175 (1.71%)	
occurrences (all)	82	97	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported