Clinical trial results:
Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Study Comparing EG-1962 to Standard of Care Oral Nimodipine in Adults with Aneurysmal Subarachnoid Hemorrhage

Summary

EudraCT number	2015-005033-53
Trial protocol	DE CZ FI DK AT
Global end of trial date	22 July 2018

Results information

Result version number	v1 (current)
This version publication date	06 December 2018
First version publication date	06 December 2018

Trial information

Trial identification

Sponsor protocol code	EG-01-1962-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02790632
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Edge Therapeutics, Inc.
Sponsor organisation address	300 Connell Dr, Ste 4000, Berkeley Heights, United States, 07922-2817
Public contact	Clinical Trial Information, Edge Therapeutics, Inc., 1 9083445257, cdandrea@edgetherapeutics.com
Scientific contact	Clinical Trial Information, Edge Therapeutics, Inc., 1 9083445257, cdandrea@edgetherapeutics.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	06 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 July 2018
Global end of trial reached?	Yes
Global end of trial date	22 July 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of intraventricular EG-1962 to standard of care oral nimodipine in subjects with aneurysmal subarachnoid hemmorhage (aSAH)

Protection of trial subjects:

Subjects were treated in Intensive Care Units

Background therapy: -

Evidence for comparator:

Oral nimodpine is the standard of care treatment for subjects with aSAH.

Actual start date of recruitment	20 June 2016
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: 164
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	New Zealand: 8
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Canada: 31
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	Germany: 41
Worldwide total number of subjects	282
EEA total number of subjects	54

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)	215
From 65 to 84 years	67
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with aneurysmal subarchnoid hemmorhage were recruited at sites located in the United States, Canada, Germany, Austria, Finland, Israel, Singapore, Hong Kong, Australia and New Zealand participated in this study. The study was open for recruitment from June 2016 to March 2018.

Pre-assignment

Screening details:

318 subjects were consented. 289 subjects were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	EG-1962

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Intraventricular nimodipine
Investigational medicinal product code	EG-1962
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraventricular use

Dosage and administration details:

A one-time infusion of EG-1962 was administered intraventricularly following repair of a ruptured saccular aneurysm.

Investigational medicinal product name	Placebo Capsules or Tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraventricular use

Dosage and administration details:

Subjects received up to 21 days of oral IP per standard of care

Arm title	Oral Nimodipine

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Oral Nimodipine Capsules or Tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received oral nimodipine up to 21 days per standard of care.

Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection
Routes of administration	Intraventricular use

Dosage and administration details:

Subjects received a one time intraventricular injection of normal saline.

Number of subjects in period 1	EG-1962	Oral Nimodipine
Started	138	144
Treated	138	144
Completed	121	128
Not completed	17	16
Adverse event, serious fatal	10	15
Consent withdrawn by subject	1	-
Lost to follow-up	6	1

Baseline characteristics

Reporting groups	
Reporting group title	EG-1962
Reporting group description: -	
Reporting group title	Oral Nimodipine
Reporting group description: -	

Reporting group values	EG-1962	Oral Nimodipine	Total
Number of subjects	138	144	282
Age categorical Units: Subjects			
Adults	138	144	282
Age continuous Units: years			
median	55.7	56.5	
full range (min-max)	22 to 75	30 to 76	-
Gender categorical Units: Subjects			
Female	95	42	137
Male	43	102	145
WFNS for randomization			
WFNS entered into IRT for stratification purposes			
Units: Subjects			
WFNS 1	0	0	0
WFNS 2	69	69	138
WFNS 3/4	69	75	144

End points

End points reporting groups	
Reporting group title	EG-1962
Reporting group description: -	
Reporting group title	Oral Nimodipine
Reporting group description: -	
Subject analysis set title	GOSE Analysis
Subject analysis set type	Full analysis
Subject analysis set description: Favorable score is 6, 7 or 8.	

Primary: GOSE	
End point title	GOSE
End point description: Glasgow Coma Scale - Extended	
End point type	Primary
End point timeframe: Day 90	

End point values	EG-1962	Oral Nimodipine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	140		
Units: Number of subjects				
number (not applicable)				
1 - Death	10	15		
2 - Vegetative State	2	6		
3 - Lower Significant Disability	28	34		
4 - Upper Significant Disability	21	16		
5 - Lower Moderate Disability	11	11		
6 - Upper Moderate Disability	27	20		
7 - Lower Good Recovery	14	11		
8 - Upper Good Recovery	23	31		
Missing	2	0		

Statistical analyses

Statistical analysis title	Analysis of GOSE Outcome
Comparison groups	EG-1962 v Oral Nimodipine

Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7381 [1]
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)

Notes:

[1] - 2-sided p-value

Secondary: MoCA

End point title	MoCA

End point description:

Montreal Cognitive Assessment

End point type	Secondary

End point timeframe:

Day 90

End point values	EG-1962	Oral Nimodipine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	111		
Units: Number of subjects				
number (not applicable)				
Favorable (>= 26)	46	51		
Unfavorable (<26)	58	60		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs occurring after randomization up to the subject's final visit were recorded

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	EG-1962

Reporting group description: -

Reporting group title	Oral Nimodipine

Reporting group description: -

Serious adverse events	EG-1962	Oral Nimodipine	
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 138 (45.65%)	69 / 144 (47.92%)	
number of deaths (all causes)	10	15	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Cerebral Ischaemia	Additional description: Delayed Cerebral Ischemia		
subjects affected / exposed	14 / 138 (10.14%)	18 / 144 (12.50%)	
occurrences causally related to treatment / all	0 / 15	0 / 19	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hydrocephalus			
subjects affected / exposed	17 / 138 (12.32%)	12 / 144 (8.33%)	
occurrences causally related to treatment / all	0 / 18	2 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral vasoconstriction	Additional description: cerebral vasospasm		
subjects affected / exposed	8 / 138 (5.80%)	18 / 144 (12.50%)	
occurrences causally related to treatment / all	0 / 9	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	9 / 138 (6.52%)	11 / 144 (7.64%)	
occurrences causally related to treatment / all	0 / 9	0 / 12	
deaths causally related to treatment / all	0 / 2	0 / 3	

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

Non-serious adverse events	EG-1962	Oral Nimodipine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	136 / 138 (98.55%)	140 / 144 (97.22%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 138 (7.25%)	10 / 144 (6.94%)	
occurrences (all)	10	11	
Hypotension			
subjects affected / exposed	9 / 138 (6.52%)	14 / 144 (9.72%)	
occurrences (all)	11	17	
Nervous system disorders			
Cerebral vasoconstriction	Additional description: cerebral vasospasm		
subjects affected / exposed	45 / 138 (32.61%)	51 / 144 (35.42%)	
occurrences (all)	46	55	
Hydrocephalus			
subjects affected / exposed	19 / 138 (13.77%)	19 / 144 (13.19%)	
occurrences (all)	21	20	
Cerebral ischaemia	Additional description: Delayed Cerebral Ischaemia		
subjects affected / exposed	21 / 138 (15.22%)	23 / 144 (15.97%)	
occurrences (all)	28	38	
Intracranial Pressure Increased			
subjects affected / exposed	24 / 138 (17.39%)	20 / 144 (13.89%)	
occurrences (all)	25	21	
Headache			
subjects affected / exposed	20 / 138 (14.49%)	14 / 144 (9.72%)	
occurrences (all)	23	15	
Cerebral Infarction			
subjects affected / exposed	9 / 138 (6.52%)	9 / 144 (6.25%)	
occurrences (all)	11	11	
Seizure			

subjects affected / exposed	12 / 138 (8.70%)	8 / 144 (5.56%)	
occurrences (all)	12	8	
Cerebral Salt Wasting Syndrome			
subjects affected / exposed	10 / 138 (7.25%)	16 / 144 (11.11%)	
occurrences (all)	10	16	
CNS Ventriculitis			
subjects affected / exposed	8 / 138 (5.80%)	4 / 144 (2.78%)	
occurrences (all)	8	4	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	45 / 138 (32.61%)	50 / 144 (34.72%)	
occurrences (all)	49	56	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 138 (5.80%)	14 / 144 (9.72%)	
occurrences (all)	8	25	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	24 / 138 (17.39%)	29 / 144 (20.14%)	
occurrences (all)	26	30	
Nausea			
subjects affected / exposed	10 / 138 (7.25%)	11 / 144 (7.64%)	
occurrences (all)	11	11	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	14 / 138 (10.14%)	14 / 144 (9.72%)	
occurrences (all)	15	14	
Agitation			
subjects affected / exposed	13 / 138 (9.42%)	11 / 144 (7.64%)	
occurrences (all)	13	11	
Delirium			
subjects affected / exposed	7 / 138 (5.07%)	6 / 144 (4.17%)	
occurrences (all)	7	6	
Renal and urinary disorders			
Urinary retention			

subjects affected / exposed	9 / 138 (6.52%)	10 / 144 (6.94%)	
occurrences (all)	9	10	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	11 / 138 (7.97%)	6 / 144 (4.17%)	
occurrences (all)	11	6	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	37 / 138 (26.81%)	34 / 144 (23.61%)	
occurrences (all)	42	38	
Pneumonia			
subjects affected / exposed	23 / 138 (16.67%)	28 / 144 (19.44%)	
occurrences (all)	24	29	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	24 / 138 (17.39%)	27 / 144 (18.75%)	
occurrences (all)	24	27	
Hypkalaemia			
subjects affected / exposed	19 / 138 (13.77%)	26 / 144 (18.06%)	
occurrences (all)	19	29	
Hypomagnesaemia			
subjects affected / exposed	9 / 138 (6.52%)	8 / 144 (5.56%)	
occurrences (all)	9	8	

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