Clinical trial results:
A randomized, double blind, double-dummy placebo controlled, 3-way cross-over study to determine the test-retest reliability of, and the effect of oral retigabine and riluzole on, peripheral motor nerve excitability measurements in patients with ALS.

Summary

EudraCT number	2015-001431-20
Trial protocol	NL
Global end of trial date	10 April 2017

Results information

Result version number	v1 (current)
This version publication date	12 March 2022
First version publication date	12 March 2022

Trial information

Trial identification

Sponsor protocol code	CHDR1417

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Centre for Human Drug Research
Sponsor organisation address	Zernikedreef 8, Leiden, Netherlands, 2333CL
Public contact	Research Director, CHDR, GGroeneveld@chdr.nl
Scientific contact	Research Director, CHDR, GGroeneveld@chdr.nl

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 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 April 2017
Global end of trial reached?	Yes
Global end of trial date	10 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the test-retest reliability of nerve excitability threshold tracking in patients with ALS.

Protection of trial subjects:

A total of 18 patients with ALS will be enrolled in the study. In order to determine test-retest reliability of the threshold tracking technique and use it as a proof-of-biology and proof-of-efficacy marker, the study has to be performed in patients with ALS. There is significant difference in parameters of excitability threshold tracking between healthy volunteers and patients with ALS. Safety will be assessed by: vital signs at each clinical visit and collection of procedure related adverse events (AEs) or serious adverse events (SAEs) throughout the study. Retigabine and riluzole are registered drugs. The safety profiles of these compounds are known. However, side effects might occur. Therefore, study drug administrations will be done in the clinic under medical supervision. Subjects will be closely monitored and will only be discharged from the unit if their medical condition allows this. As subjects will receive single doses of the two registered drugs, the risk is small and therefore acceptable compared to the (scientific) benefit.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2015
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	Netherlands: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	13
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Start 01JUN2015 in the Netherlands. . Subjects will be recruited via media advertisement or from the patientdatabase of the University Medical Centre Utrecht (UMCU), Utrecht, the Netherlands.

Pre-assignment

Screening details:

A total of 18 subjects who are patients with ALS will be enrolled into the study following satisfactory completion of a screening visit where eligibility for the study will be checked. Each subject must stop riluzole 24hrs before each occasion.

Period 1

Period 1 title	Studyperiod (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

Blinding implementation details:

The investigational drugs and their matching placebo will be indistinguishable and will be packaged in the same way.

Arms

Are arms mutually exclusive?	No
Arm title	Retigabine

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Retigabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Single dose of 300mg. Two over-encapsulated capsule of resp. 200 and 100 mg will be administered orally.

Arm title	Riluzole

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Riluzole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Single dose of 100mg. Two over-encapsulated capsules of each 50 mg will be administered orally.

Arm title	Placebo

Arm description: -

Arm type	Placebo

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

Dosage and administration details:

Single dose of two over-encapsulated placebo capsules will be administered orally.

Number of subjects in period 1	Retigabine	Riluzole	Placebo
Started	18	18	18
Completed	18	17	18
Not completed	0	1	0
Adverse event, non-fatal	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Retigabine
Reporting group description: -	
Reporting group title	Riluzole
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Retigabine	Riluzole	Placebo
Number of subjects	18	18	18
Age categorical Units: Subjects			
Age 18-80 years	18	18	18
Gender categorical Units: Subjects			
Female	1	1	1
Male	17	17	17

Reporting group values	Total		
Number of subjects	18		
Age categorical Units: Subjects			
Age 18-80 years	18		
Gender categorical Units: Subjects			
Female	1		
Male	17		

End points

End points reporting groups

Reporting group title	Retigabine
Reporting group description: -	
Reporting group title	Riluzole
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: SDTC (Stength Duration Time Constant)

End point title	SDTC (Stength Duration Time Constant)[1]
End point description:	
End point type	Primary
End point timeframe:	
Pre dose till 6h post dose	

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: See attached article for endpoints and analyses.

End point values	Retigabine	Riluzole	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	18	18	
Units: milliseconds				
arithmetic mean (standard deviation)	0.416 (± 0.064)	0.455 (± 0.058)	0.458 (± 0.080)	

Attachments (see zip file)	Kovalchuk&Heuberger_et_al-2018-

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18

Reporting groups	
Reporting group title	Retigabine
Reporting group description: -	
Reporting group title	Riluzole
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Retigabine	Riluzole	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Retigabine	Riluzole	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 18 (61.11%)	7 / 18 (38.89%)	6 / 18 (33.33%)
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Head injury			

subjects affected / exposed	0 / 18 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Limb injury			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 18 (16.67%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Headache			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Muscle contractions involuntary			
subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Somnolence			
subjects affected / exposed	5 / 18 (27.78%)	2 / 18 (11.11%)	3 / 18 (16.67%)
occurrences (all)	7	2	3
General disorders and administration site conditions			
Feeling abnormal			
subjects affected / exposed	0 / 18 (0.00%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Eye disorders			
Amblyopia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Eye symptom			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Nausea			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	1	1	0

Vomiting			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2015	Addition of a measurement during the study, called the POWERjar
17 February 2016	Change of location of fasciculations in arm in inclusion criterion, as hyperexcitability of the nerves is expected if they occur in the arms in general. Change of alcohol/drug dependence and alcohol breath test exclusion criterion, as this is not expected to impact the study validity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported