



## Clinical trial results:

### A Phase II pilot study to explore treatment with Sodium Valproate in Adults with McArdle Disease (Glycogen Storage Disorder Type V, GSDV)

#### Summary

EudraCT number	2012-002933-12
Trial protocol	GB
Global end of trial date	10 December 2018

#### Results information

Result version number	v1 (current)
This version publication date	14 March 2019
First version publication date	14 March 2019
Summary attachment (see zip file)	Valproate for McArdle disease (Sodium Valproate UK stats Report.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	11/0090
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	149, tottenham Court Road, London, United Kingdom, W1T 7NF
Public contact	Dr Ros Quinlivan, MRC Centre for Neuromuscular Disease, National hospital for neurology and Neurosurgery, 0203 4488132, r.quinlivan@ucl.ac.uk
Scientific contact	Dr Ros Quinlivan, MRC Centre for Neuromuscular Disease, National hospital for neurology and Neurosurgery, 0203 4488132, r.quinlivan@ucl.ac.uk

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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	10 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 December 2018
Global end of trial reached?	Yes
Global end of trial date	10 December 2018
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

To determine whether patients taking a medicine called sodium valproate can improve muscle function expressed by an increased number of normal muscle fibres on muscle biopsy.

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Protection of trial subjects:

An independent data monitoring committee was not deemed necessary by the sponsor. Measures to protect patients included avoidance of pre-treatment muscle biopsy if the patient had previously had one. Regular trial monitoring on the part of the sponsor. Rapid notification of SAE. All subjects were given emergency contact details of the CI and investigator and regular telephone contact with the subjects was maintained during the trial between trial visits.

Background therapy:

There was no background therapy.

Evidence for comparator:

This was an open label study, there were no comparators.

Actual start date of recruitment	01 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	United Kingdom: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

Notes:

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**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)	8
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

49 people were contacted to take part in this clinical trial. All were attending a 'highly specialized service for McArdle disease and related disorders at the National Hospital for Neurology and Neurosurgery, Queen Square, London.

### Pre-assignment

Screening details:

11 patients were screened, 2 were not eligible and one dropped out before visit 1.

8 subjects completed the study, 5 male and 3 female. Age mean 46.2 yrs (range 35-59 yrs, SD 8.4)

### Period 1

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

Blinding implementation details:

This was an open label study, there was no blinding

### Arms

Arm title	treatment
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Arm description:

there was only one arm as this was an open label study

Arm type	Experimental
Investigational medicinal product name	Sodium Valproate
Investigational medicinal product code	VPA
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Modified release VPA was prescribed at a treatment dose of 20mg/kg/day. The dose was rounded up or down to the nearest value dependent on weight.

VPA dose was titrated over 4 weeks from a starting dose of 5mg/kg/day to the treatment dose of 20mg/kg/day in order to minimise side effects.

At the end of the study VPA was titrated down over 4 weeks

Number of subjects in period 1	treatment
Started	8
16 week review	8
Completed	8

## Baseline characteristics

### Reporting groups

Reporting group title	Baseline
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Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	8	8	
Age categorical			
Mean age 46.2 years +/- 8.4 Range 35-59			
Units: Subjects			
Adults age 18-64 years	8	8	
Age continuous			
Mean age 46.2 +/- 8.4 years Range 35-59			
Units: years			
arithmetic mean	46.2		
standard deviation	± 8.4	-	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	5	5	

### Subject analysis sets

Subject analysis set title	treatment group
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Subject analysis set type	Safety analysis
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Subject analysis set description:

all trial participants received treatment

Reporting group values	treatment group		
Number of subjects	8		
Age categorical			
Mean age 46.2 years +/- 8.4 Range 35-59			
Units: Subjects			
Adults age 18-64 years	8		
Age continuous			
Mean age 46.2 +/- 8.4 years Range 35-59			
Units: years			
arithmetic mean	46.2		
standard deviation	± 8.4		
Gender categorical			
Units: Subjects			
Female			
Male			

## End points

### End points reporting groups

Reporting group title	treatment
Reporting group description: there was only one arm as this was an open label study	
Subject analysis set title	treatment group
Subject analysis set type	Safety analysis
Subject analysis set description: all trial participants received treatment	

### Primary: Workload

End point title	Workload <sup>[1]</sup>
End point description: All participants cycled on a cycle ergometer. Oxygen consumption was assessed by a face mask attached to the Cortex ergospirometry (Cortex Metalyzer II, Cortex Biophysik GmbH, Leipzig, Germany) in the UK or Quark CPET (Cosmed Srl., Milan, Italy) in DK. An incremental cycle ergometer test was performed during the screening visit (from zero to 20W in the first minute, increased by at least 5W every two minutes) to determine each participant's aerobic power (VO <sub>2</sub> peak). Heart rate (HR), monitored throughout using a 3-lead cardiac monitor, and rate of perceived exertion (RPE) were recorded every minute.	
End point type	Primary
End point timeframe: baseline-28 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: Due to the small sample size, statistical analysis was descriptive only. A statistical report has been attached	

End point values	treatment			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ml/kg/min				
arithmetic mean (standard deviation)	33.1 (± 7.6)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Muscle biopsy

End point title	Muscle biopsy
End point description: The number of muscle fibres staining positively for glycogen phosphorylase was recorded at baseline (pre-treatment muscle biopsy) and after 28 weeks (post-treatment muscle biopsy)	
End point type	Secondary
End point timeframe: Baseline and 28 weeks	

End point values	treatment			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: number of phosphorylase positive fibres				
number (not applicable)				
all patients	8			

## Statistical analyses

No statistical analyses for this end point

### Secondary: forearm exercise test

End point title	forearm exercise test
End point description: This test consisted of repetitive maximal handgrip contractions every other second for one minute (30 contractions) followed by 5min rest. Plasma lactate was analysed at 0, 2 and 5 minutes following the exercise.	
End point type	Secondary
End point timeframe: baseline, 16 weeks and 28 weeks	

End point values	treatment			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: serum lactate				
number (not applicable)	8			

## Statistical analyses

No statistical analyses for this end point

### Secondary: 12 minute walk test

End point title	12 minute walk test
End point description: A 12MWT was performed after 45 minutes of rest, following the cycle ergometer test. Participants were requested to complete as many 10m shuttle walks as possible for 12 minutes on a marked corridor.20 The total walked distance was recorded.	
End point type	Secondary
End point timeframe: baseline, 16 weeks and 28 weeks	

<b>End point values</b>	treatment			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: metres	8			

### Statistical analyses

No statistical analyses for this end point

### Secondary: SF36, physical functioning

End point title	SF36, physical functioning
End point description:	All subjects completed an SF36 questionnaire
End point type	Secondary
End point timeframe:	change from baseline, 16 weeks and 28 weeks

<b>End point values</b>	treatment			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: score	8			

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events events were documented at week 16 and 28. SAE were reported within 24 hours

Adverse event reporting additional description:

Adverse events were assessed as either not IMP related, possibly IMP related or probably IMP related

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	all patients
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Reporting group description:

All patients were enrolled into this open label trial. Adverse events were reported for all 8 patients treated with the IMP

Serious adverse events	all patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Musculoskeletal and connective tissue disorders			
painful knee	Additional description: One participant was admitted to hospital to investigate knee pain after driving for more than 16 hours. The admission lasted 14 hours. His CK was 915 IU/L on that occasion. His symptoms resolved completely. The SAE was considered not to be related		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	all patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)		
Cardiac disorders			
Ventricular extrasystoles			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	5		
Nervous system disorders			

Confusional state			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
dizziness			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
Memory impairment			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	4		
Mood altered			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	3		
Fatigue			
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	12		
Vertigo			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	3		
vivid dreams			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nerve entrapment			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
General disorders and administration site conditions			

orange urine subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Gastrointestinal disorders			
Anal fissure subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	4 / 8 (50.00%) 6		
gum disease	Additional description: bleeding gums		
subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Increased appetite subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 3		
Nausea subjects affected / exposed occurrences (all)	5 / 8 (62.50%) 8		
GI upset subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 2		
weight gain subjects affected / exposed occurrences (all)	5 / 8 (62.50%) 5		
Musculoskeletal and connective tissue disorders			
joint pain subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 3		
McArdle symptoms subjects affected / exposed occurrences (all)	8 / 8 (100.00%) 33		
swollen ankles subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Fall			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Hair disorder			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	4		
Pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
post muscle biopsy discomfort			
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	5		
Skin lesion			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Infections and infestations			
URTI			
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	5		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This was a small open label study, statistical analysis was descriptive only
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Notes: