Statsconsultancy Ltd

Address: 40 Longwood Lane, Amersham, Bucks. HP7 9EN
Email: paul@statsconsultancy.co.uk
Phone: 07905 530446
Web: www.statsconsultancy.co.uk

Statistical Report

TRIAL FULL TITLE	A phase II pilot study to explore treatment with Sodium valproate in Adults with McArdle Disease (Glycogen Storage Disorder Type V, GSDV)
REPORT OUTLINE	An analysis of the trial data from the UK site
REPORT VERSION	1.0
REPORT VERSION DATE	17th July 2018
TRIAL STATISTICIAN	Paul Bassett
REPORT AUTHOR	Paul Bassett

1 Table of Contents

2 Abbreviations and Definitions

AE	Adverse Event
GSDV	Glycogen Storage Disease Type V/ McArdle Disease
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF36	36-Item Short Form Survey

3 Introduction

3.1 Trial Background

McArdle disease (GSDV) is an inherited metabolic disorder of skeletal muscle. Affected patients are unable to produce lactate during ischaemic exercise due to a congenital lack of the enzyme muscle glycogen phosphorylase, which is essential for glycogen metabolism

McArdle disease is a rare disorder, with the incidence having been estimated to be in the region of 1:100,000. Currently, there is no satisfactory treatment for the condition.

There is some evidence from animal studies to suggest that sodium valproate can activate the gene expressing the foetal phosphorylase isoenzyme. Thus, the trial studied the effect of Sodium valproate in people with McArdle disease.

3.2 Scope of the Document

This document details an analysis from patients recruited to the UK site of the trial only. Data from the Danish site is not considered in the analyses contained with this document.

4 Study Objectives and Endpoints

4.1 Study Objectives

To determine whether treatment with Sodium valproate can cause expression of the brain isoform of glycogen phosphorylase in skeletal muscle in people with McArdle disease, who are unable to produce the muscle isoform of glycogen phosphorylase.

4.2 Endpoints

4.2.1 Primary Endpoint

The primary outcome is a measurement VO2peak, obtained during exercise endurance on a cycle ergometer. Of specific interest is the change in outcome values from Baseline to both Week 16 and Week 28.

4.2.2 Secondary Endpoints

The study has a number of secondary outcomes.

The following further physical and biochemical measurements were obtained from exercise endurance on a cycle ergometer:

- Maximum heart rate
- Workload
- Glucose – average value during exercise
- Ammonia – average value during exercise
- Lactate – maximum change from baseline/rest

Outcomes were also obtained from a 12-minute walk test:

- Total distance walked

A number of secondary outcomes were measured from a forearm exercise test:

- Ammonia – average post-baseline value
- Lactate – maximum change from baseline/rest
- Maximum hand grip strength

Outcomes from muscle biopsies:

- % fibres which stain positively for muscle glycogen phosphorylase
- % regenerative fibres

Additionally, the following secondary outcomes were collected:

- Quality of life – individual components of SF36 scores
- CK
- Drug compliance at 28 weeks (%)

- Weight gain

4.2.3 Safety Endpoints

The following safety endpoints were collected:

- Tolerability – drug levels at weeks 16 and 28
- Adverse events

5 Study Methods & General considerations

5.1 General Study Design and Plan

The trial is a Phase II open label uncontrolled pilot study to quantify the effect of sodium valproate on the study outcomes. Subjects received Sodium valproate modified release 20mg/kg/day (maximum dose 2.0g/day) was administered orally once daily for six months.

The main study measurements were made at baseline, and subsequently at weeks 16 and 28. Additionally, information on the occurrence of adverse events was collected for a further 3-months post-treatment.

5.2 Timing of Analyses

The data analysis has been performed when all patients have completed the study. The end of the trial was defined as date when the final participant recruited in the UK had completed a full dose of treatment and post one follow-up phone call at 3 months ± 14 days.

5.3 Analysis Populations

5.3.1 Full Analysis Population

The full analysis population, used for the primary trial analysis, consists of all subjects who received the study drug and who received any study drug and who participated in at least one post-baseline assessment.

5.3.2 Per Protocol Population

The Per Protocol patient group consists of all those in the Full Analysis Population whose drug compliance was between 90% and 125%.

5.3.3 Safety Population

Safety analyses were performed on all subjects who received any study treatment and are confirmed as providing complete follow-up regarding adverse event information.

5.4 Subgroups

The study recruited from two sites, the UK and Denmark. An analysis will be performed using data from both sites combined, as well as separate analyses will be of data from each site separately. As outlined in Section 3.2, only UK data is considered for this report.

5.5 Missing Data

Only observed data has been analysed. Missing data was assumed to be Missing At Random, and no imputation procedures were employed to deal with missing data.

6 Statistical Methods

6.1 Descriptive Analysis Methods

Continuous variables were summarised using the number of (non-missing) datapoints, mean and standard deviation and data range if found to follow a normal distribution. Continuous variables not found to be normally distributed were summarised by the number of datapoints, median and inter-quartile range, and data range. Categorical variables were summarised by the frequency and percentage (based on the non-missing sample size) of values in each category.

6.2 Demographic and Baseline Variables

Patient demographics consisted of measurements and age and sex. Summaries were produced for these demographics and the baseline value of all primary and secondary outcomes. The summary statistics were produced in accordance with section 6.1.

6.3 Primary Efficacy Analysis

The primary outcome is VO2peak, measured during exercise on a cycle ergometer. This was analysed descriptively only, with no formal hypothesis tests performed. Summaries at each timepoint were produced, in addition to summaries of the changes from baseline to both weeks 16 and 28. Corresponding 95% confidence intervals for the average changes over time were made. The summary statistics were produced in accordance with section 6.1.

The size of the average changes from baseline were also be calculated as a percentage of the baseline. A clinically important increase in VO2peak was defined as one that is greater than 10% of the baseline value. The clinical importance of any effects was compared to this fixed value.

The primary study analysis was performed using the Full Analysis Population (see section 5.3.1). If the Per Protocol Population (section 5.3.2) differed from this population, the analysis was repeated using this population.

6.4 Secondary Efficacy Analyses

The majority of the secondary outcomes are continuous in nature, and measured at all of baseline, week 16 and week 28. As with the primary outcome, analyses were descriptive only. Summary statistics were calculated at each timepoint, and also for the changes from baseline to weeks 16 and 28.

6.5 Safety Analyses

The main safety outcome is the occurrence of adverse events. The number of adverse events per patient was summarised.

Additionally, descriptive summary of all adverse events was produce, using the methods outlined in section 6.1. Summaries were produced for:

- Description of adverse events
- Severity (Mild, Moderate, Severe)
- Related to study participation (definite, probable, possible, unlikely, not related)

Additionally, separate summaries were produced for AEs related and not related to study participation.

7 Adherence to SAP

All analyses were performed in accordance to the methodology set out in the Statistical Analysis Plan.

8 Results

8.1 Patient demographics

The UK site recruited 8 patents into the study. The key demographics of the patient group is summarised in Table 1.

Table 1: Patient demographics

Demographic / Statistic	Summary
Age – Mean ± SD	46.2 ± 8.4
Range	35 – 59
Gender: Male – N (%)	5 (62%)
Female – N (%)	3 (38%)

The mean age of patients was 46, with a range from 35 to 59. Around two-thirds of patients were male, with a third female.

8.2 Primary Efficacy Analysis - Full Analysis Population

The primary outcome is VO2peak, measured during exercise on a cycle ergometer. This was analysed descriptively only, and summaries of the values at each timepoint are reported in Table 2. Mean changes over time are also summarised (on absolute and percentage scales), along with corresponding confidence intervals.

Table 2: Summaries of V02peak (ml/kg/min)

Timepoint	N	Mean ± SD	95% CI for mean	Range
Baseline	8	20.3 ± 4.6		12, 27
Week 16	8	21.8 ± 4.5		16, 30
Week 28	8	22.8 ± 5.5		15, 31
Change Baseline to Week 16	8	1.5 ± 2.9	-0.9, 3.9	-1, 7
Change Baseline to Week 28	8	2.5 ± 2.7	0.3, 4.7	-2, 5
% Change Baseline to Week 16	8	9.1± 15.4	-3.8, 22.0	-4.8, 33.3
% Change Baseline to Week 28	8	12.9 ± 13.9	1.3, 24.6	-9.5, 26.3

The data suggested a mean increase in V02peak from baseline to Week 16 of 1.5ml/kg/min, and a mean increase from baseline to Week 28 of 2.5 ml/kg/min. In percentage terms the mean increases were 9% and 13% from Baseline to Weeks 16 and 28 respectively.

The a priori definition of a clinical important increase was 10%. The results suggest that the increase from baseline to Week 16 did not quite meet this threshold, but the mean increase from baseline to Week 28 was greater than this threshold.

It is noted that the mean change over time have relatively wide confidence intervals. For example, the percentage change from Baseline to Week 28 ranges from 1 to 25%. This is likely to be due to the small sample size of the study.

8.3 Primary Efficacy Analysis – Per Protocol Population

The Per Protocol population consisted of those who had sufficient drug compliance. Full compliance data is given in Table 7, in Section 8.4.

At 28 weeks, no patients had a compliance below the 90% threshold. Therefore, no patient was deemed to be in the Full Analysis population, but not the Per Protocol population. As a result, the Full Analysis and Per Protocol groups are the same, and

thus the results of the Per Protocol analysis are equivalent to those of the Full Analysis population.

8.4 Secondary Efficacy Analyses

Changes over time for the secondary outcomes were also evaluated.

In addition to the primary outcome, a number of secondary outcomes were measured from the cycle test. Summaries of the measured at all of Baseline, Week 16 and Week 28 are given in Table 3, along with summaries of the changes over time from Baseline to Weeks 16 and 28.

The results suggested relatively little changes in heart rate over the course of the trial.

Increases in workload from rest to maximum value were increased slightly over the course of the study. At Week 28 values the mean increase from rest was, on average, 6W higher than at Baseline.

Glucose values showed relatively little change over the course of the trial. The change in lactate from rest to maximum showed some increase during the study. There was little change from rest to maximum at Baseline (mean = 0.03 mmol/L), but the equivalent values increased to a mean of 0.16 mmol/L and 0.13 mmol/L at Weeks 16 and 28 respectively.

Post-rest ammonia values were similar at baseline and Week 16, but showed some reduction at Week 28. There was a mean reduction of 31µmol/L from baseline to Week 28.

Table 3: Secondary outcomes from cycle test

Outcome	Timepoint	N	Mean ± SD	Range
Heart Rate (bpm)	Baseline	8	161 ± 17	135, 182
	Week 16	8	164 ± 20	125, 190
	Week 28	8	162 ± 16	132, 183
	Change Baseline to Week 16	8	4 ± 215	-20, 18
	Change Baseline to Week 28	8	1 ± 6	-9, 10
Workload (W) (*)	Baseline	8	33.1 ± 7.6	20, 40
	Week 16	8	36.3 ± 6.9	25, 40
	Week 28	8	38.8 ± 2.3	35, 40
	Change Baseline to Week 16	8	3.1 ± 8.8	-10, 20
	Change Baseline to Week 28	8	5.6 ± 7.8	0, 20
Glucose (**) (mmol/L)	Baseline	8	4.51 ± 0.41	4.13, 5.33
	Week 16	8	4.38 ± 0.30	3.83, 4.85
	Week 28	8	4.54 ± 0.37	4.10, 5.18
	Change Baseline to Week 16	8	-0.14 ± 0.38	-0.75, 0.47
	Change Baseline to Week 28	8	0.03 ± 0.59	-0.97, 0.80
Lactate (*) (mmol/L)	Baseline	8	0.03 ± 0.54	-0.90, 1.09
	Week 16	8	0.16 ± 0.49	-0.23, 1.28
	Week 28	8	0.13 ± 0.65	-0.63, 1.60
	Change Baseline to Week 16	8	0.13 ± 0.31	-0.19, 0.67
	Change Baseline to Week 28	8	0.10 ± 0.50	-0.80, 0.84
Ammonia (**) (µmol/L)	Baseline	8	137 ± 163	50, 531
	Week 16	8	140 ± 63	80, 265
	Week 28	8	106 ± 48	53, 184
	Change Baseline to Week 16	8	3 ± 115	-266, 99
	Change Baseline to Week 28	8	-31 ± 129	-348, 46

(*) Defined as maximum change from rest

(**) Defined as mean of post-rest values

Some secondary outcomes were obtained from the forearm test. A summary of the results is given in Table 4

Table 4: Secondary outcomes from the forearm test

Outcome	Timepoint	N	Mean ± SD	Range
Max grip strength (N)	Baseline	8	71 ± 35	11, 121
	Week 16	8	84 ± 25	46, 112
	Week 28	7	93 ± 31	59, 136
	Change Baseline to Week 16	8	12 ± 31	-15, 86
	Change Baseline to Week 28	7	22 ± 24	4, 72
Lactate (*) (mmol/L)	Baseline	8	-0.05 ± 0.16	-0.26, 0.18
	Week 16	8	-0.05 ± 0.23	-0.43, 0.33
	Week 28	7	0.15 ± 0.38	-0.34, 0.65
	Change Baseline to Week 16	8	-0.01 ± 0.31	-0.61, 0.59
	Change Baseline to Week 28	7	0.21 ± 0.45	-0.52, 0.78
Ammonia (**) (µmol/L)	Baseline	8	121 ± 102	45, 353
	Week 16	8	147 ± 90	52, 340
	Week 28	7	174 ± 87	43, 311
	Change Baseline to Week 16	8	26 ± 22	-13, 56
	Change Baseline to Week 28	7	43 ± 51	-42, 102

(*) Defined as maximum change from rest

(**) Defined as mean of post-rest values

Some increases in grip strength were observed. The mean value increased from 71N at Baseline, up to 84N at Week 16, and then further increased to 93N at Week 28.

Lactate values were similar at Baseline and Week 16, with little increase from rest during the measurement period. There was an increase in values at Week 28, with the mean change from rest being 0.21 mmol/L higher than at Baseline.

Ammonia values increased steadily through the trial. At Week 28, values were, on average, 43 µmol/L higher than at Baseline.

The quality of life of the patients were assessed by the SF36 questionnaire. Summaries of the values at each timepoint are given in Tables 5 and 6. This shows the result for the two main components (mental and physical), as well as the 8 individual subsections.

Table 5: Secondary outcomes from SF36 test (part 1)

Outcome	Timepoint	N	Mean ± SD	Range
Mental Component	Baseline	8	59 ± 4	51, 65
	Week 16	8	57 ± 5	50, 64
	Week 28	8	58 ± 6	44, 64
	Change Baseline to Week 16	8	−2 ± 2	−7, 1
	Change Baseline to Week 28	8	−1 ± 5	−7, 7
Physical Component	Baseline	8	45 ± 7	36, 56
	Week 16	8	47 ± 7	33, 55
	Week 28	8	46 ± 8	32, 54
	Change Baseline to Week 16	8	2 ± 5	−3, 11
	Change Baseline to Week 28	8	2 ± 7	−8, 11
Physical Functioning	Baseline	8	42 ± 7	33, 50
	Week 16	8	42 ± 7	27, 50
	Week 28	8	45 ± 6	35, 54
	Change Baseline to Week 16	8	0 ± 5	−6, 8
	Change Baseline to Week 28	8	3 ± 3	−2, 8
Role Physical	Baseline	8	50 ± 5	44, 57
	Week 16	8	52 ± 4	46, 57
	Week 28	8	52 ± 4	46, 57
	Change Baseline to Week 16	8	2 ± 2	0, 6
	Change Baseline to Week 28	8	1 ± 6	7, 13
Bodily Pain	Baseline	8	44 ± 10	22, 56
	Week 16	8	48 ± 6	38, 56
	Week 28	8	46 ± 10	34, 62
	Change Baseline to Week 16	8	3 ± 9	−9, 20
	Change Baseline to Week 28	8	2 ± 11	−17, 16

Table 6: Secondary outcomes from SF36 test (part 2)

Outcome	Timepoint	N	Mean ± SD	Range
General Health	Baseline	8	56 ± 6	46, 65
	Week 16	8	57 ± 10	34, 67
	Week 28	8	57 ± 8	39, 65
	Change Baseline to Week 16	8	1 ± 6	−12, 8
	Change Baseline to Week 28	8	0 ± 4	−7, 5
Vitality	Baseline	8	53 ± 8	41, 62
	Week 16	8	54 ± 6	44, 64
	Week 28	8	51 ± 8	41, 62
	Change Baseline to Week 16	8	1 ± 9	−15, 15
	Change Baseline to Week 28	8	−2 ± 5	−12, 6
Social Functioning	Baseline	8	55 ± 4	47, 57
	Week 16	8	53 ± 7	42, 57
	Week 28	8	53 ± 6	42, 57
	Change Baseline to Week 16	8	−2 ± 7	−15, 5
	Change Baseline to Week 28	8	−2 ± 6	−10, 5
Role emotional	Baseline	8	55 ± 2	49, 56
	Week 16	8	54 ± 4	46, 56
	Week 28	8	55 ± 4	46, 56
	Change Baseline to Week 16	8	−1 ± 3	−7, 0
	Change Baseline to Week 28	8	0 ± 1	−3, 0
Mental Health	Baseline	8	54 ± 4	46, 61
	Week 16	8	54 ± 5	48, 61
	Week 28	8	57 ± 7	43, 64
	Change Baseline to Week 16	8	0 ± 2	−3, 3
	Change Baseline to Week 28	8	3 ± 6	−3, 13

The results suggested little change the two main SF36 components (mental and physical) over the course of the trial. Additionally, there was little average change in the 8 individual subsections.

The final secondary outcomes are summarised in Table 7. The top part of the table gives summaries for variables found to be approximately normally distributed, whist variables not following a normal distribution are summarised in the bottom half.

Table 7: Summaries of other secondary outcomes

Outcome	Timepoint	N	Mean ± SD	Range
Walk test	Baseline	8	933 ± 133	683, 1100
– distance (m)	Week 16	8	958 ± 166	660, 1213
	Week 28	8	966 ± 207	606, 1253
	Change Base to Week 16	8	25 ± 215	-41, 113
	Change Base to Week 28	8	34 ± 85	-77, 153
Muscle biopsy	Baseline	7	2.2 ± 39	0.0, 10.8
– % Regenerating	Week 28	7	2.8 ± 3.2	0.5, 9.1
fibres	Change Base to Week 28	6	0.5 ± 2.4	-1.7, 4.9
Compliance (%)	Week 28	8	98.4 ± 1.6	95, 100
Weight gain (kg)	Baseline to Week 16	8	1.9 ± 2.3	-1.0, 7.0
	Baseline to Week 28	8	2.8 ± 2.9	-3.0, 5.5
Outcome	Timepoint	N	Median [IQR]	Range
Muscle biopsy	Baseline	8	0.0 [0.0 0.4]	0, 68
– % Phosph.	Week 28	7	0.3 [0.0, 2.2]	0, 41
fibres	Change Base to Week 28	7	0.0 [-0.2, 0.9]	-27, 2
CK (IU/L)	Baseline	8	868 [480, 1620]	303, 4107
	Week 16	8	561 [414, 1329]	230, 2463
	Week 28	8	648 [439, 2153]	161, 2646
	Change Base to Week 16	8	-245 [-618, 40]	-3326, 1805
	Change Base to Week 28	8	-219 [-609, 727]	-3459, 1594

There were slight increases in the distance walked in the walk test. However, the mean increase from Baseline to Week 28 was only 34m.

There was relatively little change in the percentage of phosphorylase positive fibres or regenerating fibres during the study.

CK values showed a decrease from baseline. The median reduction was over 200 IU/L from Baseline to each of Week 16 and 28.

Compliance was high, with a mean value of over 98%. The lowest level of compliance was 95%.

Over the 28 week study period, the average weight gain was 2.8kg.

8.5 Safety Analyses

The first safety outcome is the tolerability of the drug, as measured by the Sodium Valproate levels. Summaries of the drug levels are given in Table 8.

Table 8: Drug Tolerability measured by Sodium Valproate levels (mg/L)

Timepoint	N	Mean ± SD	Range
Week 16	8	73 ± 19	34, 93
Week 28	7	76 ± 26	28, 101

At both timepoints there was a mean sodium valproate value of just over 70 mg/L, with a large range from approximately 30 to 100 mg/L.

The occurrence of adverse events was also examined, and a summary of the key information is given in Table 9. This presents information on the total number of AEs, the main categorisation, seriousness, severity and the relationship to the trial drug.

There were 123 total adverse events for the 8 patients, which equates to a mean of 15 per patient.

Adverse events were categorised into groups. The most common category of adverse events was musculoskeletal, consisting of 30% of all adverse events. This was followed by 'other' (25%) and central nervous system (23%).

Of the 123 AEs, only one was classed as being a serious adverse event. This SAE was McArdle symptoms, and classified as being unlikely to be related to the study drug.

Only one AE was definitely due to the study drug, which was increased weight. A further 18 (15%) AEs were probably due to the drug. Almost two-thirds of AEs were deemed not to be related to the study drug.

Table 9: Adverse event summaries

Outcome	Category	Summary
Adverse events	Total	123
Adverse events per patient	–	15 ± 8 [4, 30]
Adverse events category	Central Nervous System	28 (23%)
	Gastrointestinal	22 (18%)
	Infection	5 (4%)
	Musculoskeletal	37 (30%)
	Other	31 (25%)
Seriousness	Not serious	122 (99%)
	Serious adverse event	1 (1%)
Severity	Mild	77 (28%)
	Moderate	28 (23%)
	Severe	16 (13%)
Relationship to drug	Definitely	1 (1%)
	Probably	18 (15%)
	Possibly	15 (12%)
	Unlikely	9 (7%)
	Not related	79 (65%)

Summary statistics are: Mean ± standard deviation [range], or number (percentage)

Full details of all adverse events are given in Table 10. This shows the number of all adverse events, and also the number of adverse events that are either definitely or probably likely, and possibly likely due to the trial drug.

Table 10: Details of all adverse events

AE category	AE details	Total Number	Number Definitely/ Probably drug related	Number Possibly drug related
Central Nervous System	Confusion	1		
	Dizziness	3		
	Forgetfulness	1		1
	Headache	2		
	Migraine	2		
	Mood changes	3		
	Tiredness & sleepiness	12	5	5
	Vertigo	3		
	Vivid Dreams	1		
Gastrointestinal	Anal fissure	1		
	Diarrhoea	6		4
	Gum problems	1		1
	Increased appetite	3	2	
	Nausea and/or vomiting	8	3	2
	Stomach upset	2		
Infection	URTI	5		
Musculoskeletal	Joint pain	3		
	McArdle symptoms	33	1	
	Swollen ankle	1		
Other	Anaemia	1		
	Bleeding	2		
	Fall	1		
	Hair loss	4	4	
	Heavy pain	1		
	Increased weight	5	4	1
	Itching	1		1
	Nerve entrapment	2		
	Orange colour urine	1		
	Post-biopsy complications	5		
	Skin lesion	2		
	Tingling (hands & toes)	1		
	Ventricular extrasystole	5		

McArdle symptoms were the most commonly occurring adverse event, with 33 instances of these. However, only one was deemed to be definitely or probably drug-related.

Tiredness and sleepiness occurred 12 times. This AE was the most common type of AE that was either definitely or probably drug-related.