EU Clinical Trials Register

Clinical trial results:

A randomised, double-blind, placebo-controlled, phase II clinical trial with a cross-over design assessing efficacy of a single dose of bumetamide in reducing focal attack severity in hypokalaemic periodic paralysis assessed using the McManis protocol.

Summary

EudraCT number	2013-004195-36
Trial protocol	GB
Global end of trial date	11 May 2017

Results information

Result version number	v1 (current)
This version publication date	28 October 2019
First version publication date	28 October 2019

Trial information

Trial identification

Sponsor protocol code	120542

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02582476
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Gower Street , London, United Kingdom, WC1E6BT
Public contact	Samim Patel, University College London , 020 76799320, samim.patel@ucl.ac.uk
Scientific contact	Dr Doreen Fialho , MRC Centre for Neuromuscular Diseases , 020 34484752, doreen.fialho@nhs.net

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	15 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 May 2017
Global end of trial reached?	Yes
Global end of trial date	11 May 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of bumetanide in reducing the severity of a focal attack of muscle weakness affecting a small hand muscle one hour after attack onset in hypokalaemic periodic paralysis.

Protection of trial subjects:

This study was conducted in accordance with the final protocol and in compliance with all local regulatory requirements and laws. Subject Information and Written Informed Consent was obtained before initiation of any protocol-specified activities. The investigator explained the nature, purpose, and possible risks associated with study participation to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document. All subject were assessed in a hospital setting under strict monitoring by nurses and doctors. Rescue treatment for acute attacks of weakness (typical for the condition) were readily available if needed.

Background therapy:

Subjects were allowed to take oral potassium for the duration of the trial as per standard of care. Subjects withheld carbonic anhydrase inhibitor medications and anti-inflammatory medication for 72 hours prior to assessment visit. Subjects started their usual medication as soon as the visit ended. Subjects were allowed to continue any other periodic paralysis or other medical treatments for the duration of the trial.

Evidence for comparator:

To provide class 1 evidence for the efficacy of treatment with Bumetanide in this patient population.

Actual start date of recruitment	15 January 2015
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 Kingdom: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled in February 2015. In May 2017 the study was terminated early due to slow recruitment and expiring funding. Subjects were invited by post, during their appointment at the channelopathy clinic at the National Hospital for Neurology and Neurosurgery in London and at their neurophysiology appointment at the same hospital

Pre-assignment

Screening details:

11 subjects were screened. One subject failed screening due to absence of HypoPP mutation (inclusion criterion).

Period 1

Period 1 title	Visit 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Over-encapsulated bumetanide and matching placebo

Arms

Are arms mutually exclusive?	Yes
Arm title	Bumetanide V1 - Placebo V2

Arm description:

Subjects who received Bumetanide in visit 1 and placebo in visit 2

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

Dosage and administration details:

single dose 2mg

Arm title	Placebo V1 - Bumetanide V2

Arm description:

Subjects who received placebo in visit 1 and Bumetanide in visit 2

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

Number of subjects in period 1	Bumetanide V1 - Placebo V2	Placebo V1 - Bumetanide V2
Started	5	5
Completed	5	5

Period 2

Period 2 title	Washout period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

No IMP given

Arms

Are arms mutually exclusive?	Yes
Arm title	Bumetanide V1 - Placebo 2

Arm description:

Subjects who received Bumetanide in visit 1 and placebo in visit 2

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo V1 - Bumetanide V2

Arm description:

Subjects who received placebo in visit 1

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Bumetanide V1 - Placebo 2	Placebo V1 - Bumetanide V2
Started	5	5
Completed	4	5
Not completed	1	0
Pregnancy	1	-

Period 3

Period 3 title	Visit 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Over-encapsulated bumetanide and matching placebo

Arms

Are arms mutually exclusive?	Yes
Arm title	Bumetanide V1 - Placebo V2

Arm description:

Subjects who received Bumetanide in visit 1 and placebo in visit 2

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

Arm title	Placebo V1 - Bumetanide V2

Arm description:

Subjects who received placebo in visit 1 and Bumetanide in visit 2

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

Dosage and administration details:

single dose 2mg

Number of subjects in period 3	Bumetanide V1 - Placebo V2	Placebo V1 - Bumetanide V2
Started	4	5
Completed	4	5

Baseline characteristics

Reporting groups

Reporting group title	Visit 1

Reporting group description: -

Reporting group values	Visit 1	Total	
Number of subjects	10	10	
Age categorical			
Age was collected at the screening visit.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	10	10	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Median age for all participants was 45 years. Age range 18-55 years.			
Units: years			
median	45		
full range (min-max)	18 to 55	-	
Gender categorical			
3 female and 7 male participants were recruited.			
Units: Subjects			
Female	3	3	
Male	7	7	

Subject analysis sets

Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Placebo

Subject analysis set title	Bumetanide
Subject analysis set type	Full analysis

Subject analysis set description:

Treatment with Bumetanide

Reporting group values	Placebo	Bumetanide	
Number of subjects	9	10	
Age categorical			
Age was collected at the screening visit.			
Units: Subjects			

In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	9	10	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Median age for all participants was 45 years. Age range 18-55 years.			
Units: years			
median	47	45	
full range (min-max)	18 to 55	18 to 55	
Gender categorical			
3 female and 7 male participants were recruited.			
Units: Subjects			
Female	2	3	
Male	7	7	

End points

End points reporting groups

Reporting group title	Bumetanide V1 - Placebo V2
Reporting group description:	
Subjects who received Bumetanide in visit 1 and placebo in visit 2	
Reporting group title	Placebo V1 - Bumetanide V2
Reporting group description:	
Subjects who received placebo in visit 1 and Bumetanide in visit 2	
Reporting group title	Bumetanide V1 - Placebo 2
Reporting group description:	
Subjects who received Bumetanide in visit 1 and placebo in visit 2	
Reporting group title	Placebo V1 - Bumetanide V2
Reporting group description:	
Subjects who received placebo in visit 1	
Reporting group title	Bumetanide V1 - Placebo V2
Reporting group description:	
Subjects who received Bumetanide in visit 1 and placebo in visit 2	
Reporting group title	Placebo V1 - Bumetanide V2
Reporting group description:	
Subjects who received placebo in visit 1 and Bumetanide in visit 2	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Placebo	
Subject analysis set title	Bumetanide
Subject analysis set type	Full analysis
Subject analysis set description:	
Treatment with Bumetanide	

Primary: Focal attack severity one hour after treatment

End point title	Focal attack severity one hour after treatment
End point description:	
This was measured as CMAP amplitude expressed as a percent of peak CMAP during or after the McManis exercise 1 hour following IMP intake.	
End point type	Primary
End point timeframe:	
The effect of treatment on focal attack severity one hour after treatment intake.	

End point values	Placebo	Bumetanide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	10		
Units: Percentage				
arithmetic mean (confidence interval 95%)				
CMAP amplitude	34.9 (28.1 to 41.7)	40.6 (33.6 to 47.6)		

Attachments (see zip file)	Normal QQ plot of residuals/Normal QQ plot of residuals.png
	Scatter plot of the residuals/Scatter plot of the residuals.png
	Normality checks for the primary outcome/Normality checks for

Statistical analyses

Statistical analysis title	Primary Outcome Analysis

Statistical analysis description:

The primary outcome is the CMAP amplitude relative to the peak value one hour after the administration of treatment. Treatment is administered when the CMAP amplitude reaches 60% of its peak value.

Comparison groups	Placebo v Bumetanide
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	0.059
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.057
upper limit	0.175
Variability estimate	Standard error of the mean
Dispersion value	0.049

Notes:

[1] - Nine participants completed both trial visits and received both placebo and bumetanide. The mean effect difference calculation was therefore based on these 9 participants. (One participant only received Bumetanide.)

Secondary: Focal attack duration

End point title	Focal attack duration

End point description:

This was measured as the time between treatment administration until CMAP returns to 65% of peak CMAP within 4 hours following the treatment intake

End point type	Secondary

End point timeframe:

4 hours following IMP intake

End point values	Placebo	Bumetanide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9[2]	10		
Units: Minutes				
arithmetic mean (standard deviation)				
Minutes	999 (± 0)	133 (± 151.3)		

Notes:

[2] - NONE OF THE PARTICIPANTS RETURNED TO 65% OF PEAK VALUE WITHIN 4 HOURS (NO DATA AVAILABLE)

Statistical analyses

Statistical analysis title	Attack duration

Statistical analysis description:

Attack duration has been defined as time in minutes between treatment administration until CMAP returns to 65% peak value.

Comparison groups	Bumetanide v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.05 [4]
Method	Descriptive
Parameter estimate	Mean

Notes:

[3] - None of the participants in the placebo group reached this endpoint, therefore it was not possible to analyse this outcome.
Two patients reached this outcome after administration of Bumetanide at 240 and 26 minutes after IMP intake respectively.

[4] - Descriptive analysis only, p-value is not available

Secondary: The initial effect of treatment on severity of a focal attack

End point title	The initial effect of treatment on severity of a focal attack

End point description:

The effect of treatment on severity of a focal attack within the first two hours (0-2). This will be measured as CMAP amplitude (in percent compared to peak) area under the curve (AUC) from treatment administration until two hours post-treatment.

End point type	Secondary

End point timeframe:

The initial effect of treatment on severity of a focal attack within the first two hours post treatment

End point values	Placebo	Bumetanide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	10		
Units: Percentage				
arithmetic mean (confidence interval 95%)				
Percentage	37 (30.9 to 42.7)	41 (36.2 to 45.7)		

Statistical analyses

Statistical analysis title	The initial effect of treatment

Statistical analysis description:

The initial effect was analysed using the same regression model as per the primary outcome.

Comparison groups	Bumetanide v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.048
upper limit	0.133
Variability estimate	Standard error of the mean

Notes:

[5] - Nine participants completed both trial visits and received both placebo and bumetanide.
Total sample: n=9

Secondary: The late effect of treatment on severity of a focal attack

End point title	The late effect of treatment on severity of a focal attack

End point description:

The effect of treatment on severity of a focal attack within the last 2 hours (3-4). This will be measured as CMAP amplitude (in percent) AUC from treatment administration during the third and the fourth hours post-treatment.

End point type	Secondary

End point timeframe:

The late effect of treatment on severity of a focal attack two to four hours post treatment

End point values	Placebo	Bumetanide		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	10		
Units: Percentage				
arithmetic mean (confidence interval 95%)				
Percentage	31 (25.5 to 37.2)	40 (32.9 to 46.5)		

Statistical analyses

Statistical analysis title	The late effect of treatment
Statistical analysis description: The late treatment effect was analysed using the same regression model as per the primary outcome.	
Comparison groups	Placebo v Bumetanide
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	0.085
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.021
upper limit	0.191
Variability estimate	Standard error of the mean

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
From the treatment visit until follow up telephone call	
Adverse event reporting additional description:	
Adverse events were reviewed during the study visits following treatment intake. They were also assessed by a phone call consultation seven days following each study visit.	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Bumetanide Treatment Visit
Reporting group description:	
Adverse events observed/recorded by the researcher and reported by the participant during the period of direct observation before and after treatment intake (between 5-7hours)	
Reporting group title	Placebo Treatment Visit
Reporting group description:	
Adverse events observed/recorded by the researcher and reported by the participant during the period of direct observation before and after treatment intake (between 5-7hours)	
Reporting group title	Placebo Treatment Phone Call
Reporting group description:	
Adverse events reported by the participant during one week after treatment intake following discharge. Information obtained via phone call.	
Reporting group title	Bumetanide Treatment Phone Call
Reporting group description:	
Adverse events reported by the participant during one week after treatment intake following discharge. Information obtained via phone call.	

Serious adverse events	Bumetanide Treatment Visit	Placebo Treatment Visit	Placebo Treatment Phone Call
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Bumetanide Treatment Phone Call		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Bumetanide Treatment Visit	Placebo Treatment Visit	Placebo Treatment Phone Call
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	8 / 9 (88.89%)	6 / 9 (66.67%)
Investigations			
Haematoma	Additional description: Small haematoma after cannula removal. Not clinically significant.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Bradychardia	Additional description: Asymptomatic bradycardia - not clinically significant.		
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
tingling			
subjects affected / exposed	1 / 10 (10.00%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	1	2	0
Headache			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Paresis	Additional description: Atypical attack of muscle weakness not due to the underlying diagnosis of periodic paralysis.		
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash	Additional description: Skin rash: reaction to cannula plaster		
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Micturition disorder	Additional description: Increased micturition.		
subjects affected / exposed	6 / 10 (60.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	6	0	0
Hypokalaemia	Additional description: Electrolyte imbalance.		

subjects affected / exposed	3 / 10 (30.00%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	3	2	0

Musculoskeletal and connective tissue disorders

Muscle Stiffness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Burning sensation	Additional description: Burning pain while performing hand exercise.		
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Paralysis	Additional description: Acute/transitory muscle weakness attack related to the diagnosis of periodic paralysis. This is an expected recurrent symptom in this disorder. Includes focal and generalised weakness attacks.		
subjects affected / exposed	7 / 10 (70.00%)	5 / 9 (55.56%)	5 / 9 (55.56%)
occurrences (all)	7	5	7
Muscle swelling	Additional description: "Muscle soreness": reported by participants at phone call consultations, recorded using their own words.		
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1

Infections and infestations

Cold symptoms			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	1	1	1

Non-serious adverse events	Bumetanide Treatment Phone Call		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 10 (60.00%)		
Investigations			
Haematoma	Additional description: Small haematoma after cannula removal. Not clinically significant.		
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Bradychardia	Additional description: Asymptomatic bradycardia - not clinically significant.		
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
tingling			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

Headache			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Paresis	Additional description: Atypical attack of muscle weakness not due to the underlying diagnosis of periodic paralysis.		
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash	Additional description: Skin rash: reaction to cannula plaster		
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Micturition disorder	Additional description: Increased micturition.		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Hypokalaemia	Additional description: Electrolyte imbalance.		
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Muscle Stiffness			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Burning sensation	Additional description: Burning pain while performing hand exercise.		
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Paralysis	Additional description: Acute/transitory muscle weakness attack related to the diagnosis of periodic paralysis. This is an expected recurrent symptom in this disorder. Includes focal and generalised weakness attacks.		
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	5		
Muscle swelling	Additional description: "Muscle soreness": reported by participants at phone call consultations, recorded using their own words.		
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Infections and infestations			

Cold symptoms			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2014	Substantial amendment to reply to the comments raised by the ethics committee
27 July 2015	Substantial amendment 2 to advertise the trial through a patient association to accelerate recruitment
04 January 2016	Substantial amendment to clarify screening visit and include news flash advertisement by MDC
16 June 2016	Amendment made following a pregnancy
11 November 2016	Substantial amendment to allow patients to be re-consented remotely

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported