Clinical trial results:
A double blind, randomized, placebo controlled, crossover study of the effectiveness of oral fampridine in improving upper limb function in progressive multiple sclerosis.

Summary

EudraCT number	2011-002561-38
Trial protocol	IE
Global end of trial date	16 February 2016

Results information

Result version number	v1 (current)
This version publication date	13 March 2021
First version publication date	13 March 2021

Trial information

Trial identification

Sponsor protocol code	SVUHneuro002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	St. Vincent's University Hospital
Sponsor organisation address	Elm Park, Dublin, Ireland,
Public contact	Dr. Christopher McGuigan, St. Vincent's University Hospital, 00353 12214179, C.Mcguigan@st-vincents.ie
Scientific contact	Dr. Christopher McGuigan, St. Vincent's University Hospital, 00353 12214179, C.Mcguigan@st-vincents.ie

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	04 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 February 2016
Global end of trial reached?	Yes
Global end of trial date	16 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of treatment with fampridine in patients with secondary progressive MS (SPMS) or primary progressive MS (PPMS) with upper limb dysfunction (as defined by a 9-HPT time of between 15-90 seconds) and Kurtzke EDSS scores in the range 4.0-7.0 on
1. Upper limb function assessed by the nine-hole peg test (9-HPT) and the Jebson Taylor Hand Function Test (JTT).
2. Scores of the MSIS-29 (physical), MSWS-12 and the Disabilities of the Arm, Shoulder and Hand Score (DASH)

Protection of trial subjects:

Patients were reviewed at every trial visit by medical professionals with experience in MS. Direct contact details for trial investigators were given to the patient. General practitioners were informed about the patient's participation in the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2012
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	Ireland: 64
Worldwide total number of subjects	64
EEA total number of subjects	64

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)	57
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study recruited male and female patients between the ages of 18 – 70 years with clinically definite primary or secondary progressive multiple sclerosis. Patients will be identified in and recruited from the multiple sclerosis clinics in St. Vincent's University Hospital, Dublin, Ireland.

Pre-assignment

Screening details:

Eligibility criteria were assessed during a separate screening visit.

Period 1

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

Blinding implementation details:

Procedure for blinding of Fampridine versus placebo:
Fampridine and placebo capsules looked identical.
Fampridine and placebo were packaged in identical packaging.
The label instructions were identical for both.
The study was conducted in a double-blind fashion. Study treatment assignment was blinded for both the investigators and the subject.
The study pharmacist retained the list of fampridine and placebo product codes.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description: -

Arm type	Experimental and control
Investigational medicinal product name	Fampridine
Investigational medicinal product code	
Other name	4-Aminopyridine, Fampyra
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 10 mg tablet twice daily

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

Dosage and administration details:

One tablet twice daily

Arm title	Arm B

Arm description: -

Arm type	Experimental and control

Investigational medicinal product name	Fampridine
Investigational medicinal product code	
Other name	4-Aminopyridine, Fampyra
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: One 10 mg tablet twice daily	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: One tablet twice daily	

Number of subjects in period 1	Arm A	Arm B
Started	36	28
Completed	36	28

Period 2	
Period 2 title	Outcome Period 1
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Assessor, Subject
Arms	
Are arms mutually exclusive?	Yes
Arm title	Arm A
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Fampridine
Investigational medicinal product code	
Other name	4-Aminopyridine, Fampyra
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: One 10 mg tablet twice daily	
Arm title	Arm B
Arm description: -	
Arm type	Placebo

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

Dosage and administration details:

One tablet twice daily

Number of subjects in period 2	Arm A	Arm B
Started	36	28
Completed	35	28
Not completed	1	0
Lost to follow-up	1	-

Period 3

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet twice daily

Arm title	Arm B

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Fampridine
Investigational medicinal product code	
Other name	4-Aminopyridine, Fampyra
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 10 mg tablet twice daily

Number of subjects in period 3	Arm A	Arm B
Started	35	28
Completed	33	28
Not completed	2	0
Lost to follow-up	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description: -	
Reporting group title	Arm B
Reporting group description: -	

Reporting group values	Arm A	Arm B	Total
Number of subjects	36	28	64
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	55.1	53.7	
inter-quartile range (Q1-Q3)	45.1 to 59.5	45.4 to 60.9	-
Gender categorical Units: Subjects			
Female	23	15	38
Male	13	13	26
Unknown	0	0	0
MS Subtype Units: Subjects			
Secondary Progressive MS	23	22	45
Primary Progressive MS	13	5	18
Unknown	0	1	1
On DMT Units: Subjects			
Yes	12	13	25
No	23	14	37
Unknown	1	1	2
Baclofen Units: Subjects			
No	32	24	56
Yes	4	4	8
Tizanidine Units: Subjects			
No	33	27	60

Yes	3	1	4
Benzo Units: Subjects			
No	36	27	63
Yes	0	1	1
Disease duration Units: years			
median	15.7	19.2	
inter-quartile range (Q1-Q3)	9.9 to 24.6	9.0 to 25.4	-

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: -	
Reporting group title	Arm B
Reporting group description: -	
Reporting group title	Arm A
Reporting group description: -	
Reporting group title	Arm B
Reporting group description: -	
Reporting group title	Arm A
Reporting group description: -	
Reporting group title	Arm B

Reporting group description: -

Primary: Upper limb response to treatment by 9-hole peg test (dominant hand)

End point title	Upper limb response to treatment by 9-hole peg test (dominant hand)[1]

End point description:

An upper limb responder to fampridine was defined as a patient with both of the two "on treatment" 9-HPT assessments (assessments 4 & 5 or 7 & 8) improving 20% from the average of the baseline assessments (1, 2 & 3).

End point type	Primary

End point timeframe:

At 4 and 8 weeks after baseline combined

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: Insufficient positive cases to allow for reliable statistical analysis. As outlined in previous responses based on statistical analysis plan, we were unable to proceed to analysis due to the low number of responders.

End point values	Arm A	Arm B	Arm A	Arm B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	28	34	27
Units: subjects				
Response	2	0	3	2
No response	33	28	31	25

Statistical analyses

No statistical analyses for this end point

Primary: Upper limb response to treatment by 9-hole peg test (non-dominant hand)

End point title	Upper limb response to treatment by 9-hole peg test (non-dominant hand)[2]

End point description:

An upper limb responder to fampridine was defined as a patient with both of the two "on treatment" 9-HPT assessments (assessments 4 & 5 or 7 & 8) improving 20% from the average of the baseline assessments (1, 2 & 3).

End point type	Primary

End point timeframe:

At 4 and 8 weeks after baseline combined

Notes:

[2] - 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: Insufficient positive cases to allow for reliable statistical analysis. As outlined in previous responses based on statistical analysis plan, we were unable to proceed to analysis due to the low number of responders.

End point values	Arm A	Arm B	Arm A	Arm B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	28	34	27
Units: subjects				
Response	0	1	0	2
No response	35	27	34	25

Statistical analyses

No statistical analyses for this end point

Secondary: Upper limb response Jebsen Taylor Hand Function Test (dominant hand)

End point title	Upper limb response Jebsen Taylor Hand Function Test (dominant hand)

End point description:

A secondary measure of upper limb responsiveness will be defined as a 20% improvement in from baseline in the average time taken to complete all seven tasks on the JTT "on treatment" (assessments 4 & 5 or 7 & 8) compared with baseline assessments (assessments 1,2 & 3).

End point type	Secondary

End point timeframe:

At 4 and 8 weeks after baseline combined

End point values	Arm A	Arm B	Arm A	Arm B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	28	33	28
Units: subjects				
Response	3	0	0	0
No response	32	28	33	28

Statistical analyses

No statistical analyses for this end point

Secondary: Upper limb response Jebsen Taylor Hand Function Test (non-dominant hand)

End point title	Upper limb response Jebsen Taylor Hand Function Test (non-dominant hand)

End point description:

A secondary measure of upper limb responsiveness will be defined as a 20% improvement in from baseline in the average time taken to complete all seven tasks on the JTT "on treatment" (assessments 4 & 5 or 7 & 8) compared with baseline assessments (assessments 1,2 & 3).

End point type	Secondary

End point timeframe:

At 4 and 8 weeks after baseline

End point values	Arm A	Arm B	Arm A	Arm B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	28	33	28
Units: subjects				
Response	2	0	0	1
No response	33	28	33	27

Statistical analyses

No statistical analyses for this end point

Secondary: Response Timed 25 Foot Walk

End point title	Response Timed 25 Foot Walk

End point description:

b) A mobility responder to fampridine will be defined as a patient with both of the two "on treatment" T25FW assessments (assessments 4 & 5 or 7 & 8) being better than the maximum of any of the four "off treatment" assessments (assessments 1, 2, 3, & 9). Otherwise the patient will be deemed a non-responder.

End point type	Secondary

End point timeframe:

At 4 and 8 weeks after baseline combined and 12 weeks after second baseline

End point values	Arm A	Arm B	Arm A	Arm B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	27	34	26
Units: subjects				
Response	35	27	32	24
No response	0	0	2	2

Statistical analyses

No statistical analyses for this end point

Secondary: Change in DASH over time

End point title	Change in DASH over time

End point description:

Change in DASH over time across two periods. Values represent the mean difference of fampridine treatment in reference to placebo.

End point type	Secondary

End point timeframe:

Over 8 weeks after baseline

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	27		
Units: points				
arithmetic mean (standard error)	-1.65 (± 5.28)	-1.65 (± 5.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in AMSQ over time

End point title	Change in AMSQ over time

End point description:

Change in AMSQ over time across two periods. Values represent the mean difference of fampridine treatment in reference to placebo.

End point type	Secondary

End point timeframe:

Over 8 weeks after baseline

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	27		
Units: points				
arithmetic mean (standard error)	3.98 (± 5.52)	3.98 (± 5.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in MSWS over time

End point title	Change in MSWS over time

End point description:

Change in MSWS over time across two periods. Values represent the mean difference of fampridine treatment in reference to placebo.

End point type	Secondary

End point timeframe:

Over 8 weeks from baseline

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	27		
Units: points				
arithmetic mean (standard error)	1.26 (± 7.14)	1.25 (± 7.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in MSIS-20 over time

End point title	Change in MSIS-20 over time

End point description:

Change in MSIS-20 over time across two periods. Values represent the mean difference of fampridine treatment in reference to placebo.

End point type	Secondary

End point timeframe:

Over 8 weeks after baseline

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	27		
Units: points				
arithmetic mean (standard error)	-1.04 (± 6.04)	-1.04 (± 6.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in MSIS-9 over time

End point title	Change in MSIS-9 over time

End point description:

Change in MSIS-9 over time across two periods. Values represent the mean difference of fampridine treatment in reference to placebo.

End point type	Secondary

End point timeframe:

Over 8 weeks after baseline

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	27		
Units: points				
arithmetic mean (standard error)	4.15 (± 5.69)	4.15 (± 5.69)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 22 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	NA
Reporting groups	
Reporting group title	Fampridine
Reporting group description: Subjects while on fampridine treatment	
Reporting group title	Placebo
Reporting group description: Subjects on placebo treatment	

Serious adverse events	Fampridine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 64 (0.00%)	0 / 64 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Fampridine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 64 (50.00%)	25 / 64 (39.06%)	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	3 / 64 (4.69%)	4 / 64 (6.25%)	
occurrences (all)	3	4	
Injury, poisoning and procedural complications			
Laceration to foot			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Fall			

subjects affected / exposed	1 / 64 (1.56%)	2 / 64 (3.13%)	
occurrences (all)	1	2	
Vascular disorders			
Peripheral venous disease			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 64 (7.81%)	4 / 64 (6.25%)	
occurrences (all)	5	4	
Headache			
subjects affected / exposed	7 / 64 (10.94%)	0 / 64 (0.00%)	
occurrences (all)	7	0	
Worsening hemiparesis			
subjects affected / exposed	2 / 64 (3.13%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
Muscle spasticity			
subjects affected / exposed	2 / 64 (3.13%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Numbness			
subjects affected / exposed	0 / 64 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Paresthesia			
subjects affected / exposed	4 / 64 (6.25%)	0 / 64 (0.00%)	
occurrences (all)	4	0	
Tremor			
subjects affected / exposed	2 / 64 (3.13%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
Syncope			
subjects affected / exposed	3 / 64 (4.69%)	0 / 64 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	1 / 64 (1.56%)	2 / 64 (3.13%)	
occurrences (all)	1	2	
Thrombocytosis			

subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	3 / 64 (4.69%)	1 / 64 (1.56%)	
occurrences (all)	3	1	
Insomnia			
subjects affected / exposed	1 / 64 (1.56%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Weakness			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 64 (6.25%)	0 / 64 (0.00%)	
occurrences (all)	4	0	
Vomiting			
subjects affected / exposed	1 / 64 (1.56%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	1 / 64 (1.56%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	0 / 64 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 64 (3.13%)	0 / 64 (0.00%)	
occurrences (all)	2	0	

Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Mobility decreased			
subjects affected / exposed	1 / 64 (1.56%)	3 / 64 (4.69%)	
occurrences (all)	1	3	
Muscular pain			
subjects affected / exposed	2 / 64 (3.13%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Pain extremity			
subjects affected / exposed	2 / 64 (3.13%)	3 / 64 (4.69%)	
occurrences (all)	2	3	
Hip pain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Ear Infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Urinary Tract Infection			
subjects affected / exposed	2 / 64 (3.13%)	3 / 64 (4.69%)	
occurrences (all)	2	3	
Sinusitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	5 / 64 (7.81%)	0 / 64 (0.00%)	
occurrences (all)	5	0	

Lower respiratory tract infection subjects affected / exposed occurrences (all)	2 / 64 (3.13%) 2	1 / 64 (1.56%) 1	
Influenza subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	0 / 64 (0.00%) 0	

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