



Clinical trial results:

EFFICACY OF EGb 761® 120 mg bid VERSUS PLACEBO IN PATIENTS SUFFERING FROM FRIEDREICH ATAXIA A 3 months, phase II, randomised, double blind, placebo-controlled, parallel groups, clinical study.

Summary

EudraCT number	2007-005371-34
Trial protocol	FR
Global end of trial date	20 October 2011

Results information

Result version number	v1 (current)
This version publication date	05 May 2016
First version publication date	05 May 2016

Trial information

Trial identification

Sponsor protocol code	2-39-00240-133
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00824512
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Pharma
Sponsor organisation address	65 Quai George Gorse, Boulogne-Billancourt, Cedex, France, 92100
Public contact	Medical Director, Neurology, Ipsen Pharma, clinical.trials@ipsen.com
Scientific contact	Medical Director, Neurology, Ipsen Pharma, clinical.trials@ipsen.com

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	12 June 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 October 2011
Global end of trial reached?	Yes
Global end of trial date	20 October 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate an improvement in skeletal muscle energetics and particularly in mitochondrial oxidative phosphorylation.

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 June 2008
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	France: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	17
Adults (18-64 years)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at a single centre investigational site in France.

Pre-assignment

Screening details:

From the 22 randomised patients, 21 were included in the modified Intention-To-Treat (mITT) population. 1 patient in the placebo group did not meet the primary criteria and thus excluded from the analysis. All patient were included in the safety population.

Period 1

Period 1 title	mITT population (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Egb 761® 120 mg

Arm description:

Egb 761 120 mg : Egb 761® 120 mg BID, orally for 12 to 14 weeks

Arm type	Experimental
Investigational medicinal product name	EGb 761 (r) 120 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Buccal tablet
Routes of administration	Oral use

Dosage and administration details:

120 mg

Arm title	Placebo
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Arm description:

Placebo : Placebo 1 tablet BID, orally for 12 to 14 weeks

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:

NA

Number of subjects in period 1 ^[1]	Egb 761® 120 mg	Placebo
Started	11	10
Completed	11	10

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Worldwide details are for all randomized subjects, however baseline details are for mITT population (1 subject in Placebo arm was excluded from the mITT population due to Test or examination not done)

Baseline characteristics

Reporting groups

Reporting group title	Egb 761® 120 mg
Reporting group description: Egb 761 120 mg : Egb 761® 120 mg BID, orally for 12 to 14 weeks	
Reporting group title	Placebo
Reporting group description: Placebo : Placebo 1 tablet BID, orally for 12 to 14 weeks	

Reporting group values	Egb 761® 120 mg	Placebo	Total
Number of subjects	11	10	21
Age categorical Units: Subjects			
12-15 years	5	4	9
16-22 years	6	6	12
Age continuous Units: years			
median	16	16	
full range (min-max)	12 to 20	12 to 22	-
Gender categorical Units: Subjects			
Female	5	5	10
Male	6	5	11
Duration since first symptoms Units: Years			
median	8.1	7.7	
full range (min-max)	3 to 15	4 to 18	-
Number of repeats of Guanine Adenine Adenine (GAA) sequence Units: GAA sequence repetitions			
median	700	810	
full range (min-max)	500 to 950	100 to 1000	-

End points

End points reporting groups

Reporting group title	EGb 761® 120 mg
Reporting group description: EGb 761 120 mg : EGb 761® 120 mg BID, orally for 12 to 14 weeks	
Reporting group title	Placebo
Reporting group description: Placebo : Placebo 1 tablet BID, orally for 12 to 14 weeks	

Primary: Creatine Rephosphorylation Rate Post Exercise

End point title	Creatine Rephosphorylation Rate Post Exercise
End point description: The primary efficacy endpoint is the evolution of the Creatine Rephosphorylation rate post-exercise corrected by pH (sec-1) using Phosphorus 31 Nuclear Magnetic Resonance (P-31 NMR) spectroscopy between the W0 and W12 visits. As this study is evaluating an orphan pathology with only few patients in France known to be affected by Friedreich ataxia, and considering there are no specific studies in this population with EGb761, the use of a statistical hypothesis for a sample size calculation was not possible. Primary efficacy analyses performed on the mITT population and analysis of safety performed on the safety population.	
End point type	Primary
End point timeframe: Baseline (Week 0) to Week 12	

End point values	EGb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: pH per second				
median (full range (min-max))				
Baseline (Week 0)	0.024 (0.013 to 0.037)	0.029 (0.018 to 0.04)		
Week 12	0.022 (0.015 to 0.043)	0.029 (0.014 to 0.035)		
Change from Baseline (Week 0) to Week 12	0.001 (-0.009 to 0.009)	0 (-0.013 to 0.005)		

Statistical analyses

Statistical analysis title	Creatine Rephosphorylation Rate Post Exercise
Comparison groups	EGb 761® 120 mg v Placebo

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9133
Method	Non parametric ANCOVA on the rank test

Secondary: Peak Post Exercise Perfusion

End point title	Peak Post Exercise Perfusion
End point description: Peak post exercise perfusion (mL/mn/100 g of tissue) was assessed using Arterial spin labelling combined with Nuclear Magnetic Resonance imaging.	
End point type	Secondary
End point timeframe: Baseline (Week 0) to Week 12	

End point values	Egb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: ml/mn/100 g of tissue				
median (full range (min-max))				
Baseline (Week 0)	54.3 (33.9 to 91)	51.8 (10.8 to 81.4)		
Week 12	58.8 (37.6 to 88.8)	46.6 (30.7 to 63.1)		
Change from Baseline (Week 0) to Week 12	3.6 (-29.5 to 31.2)	-1.55 (-20.9 to 23.2)		

Statistical analyses

Statistical analysis title	Peak Post Exercise Perfusion
Comparison groups	Egb 761® 120 mg v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0661
Method	Non parametric ANCOVA on the rank test

Secondary: Time to Peak Perfusion

End point title	Time to Peak Perfusion
End point description:	
End point type	Secondary

End point timeframe:

Baseline (Week 0) to Week 12

End point values	EGb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: seconds				
median (full range (min-max))				
Baseline (Week 0)	38.3 (0.8 to 269.3)	58.55 (5.3 to 317.3)		
Week 12	39.8 (0.8 to 119.3)	76.55 (0.8 to 384.8)		
Change from Baseline (Week 0) to Week 12	8.5 (-267 to 94.5)	14.25 (-232.5 to 274.5)		

Statistical analyses

Statistical analysis title	Time to Peak Perfusion
Comparison groups	EGb 761® 120 mg v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2725
Method	Non parametric ANCOVA on the rank test

Secondary: Perfusion-time Integral During the First 9 Minutes Post Exercise

End point title	Perfusion-time Integral During the First 9 Minutes Post Exercise
End point description:	The integral of 'peak perfusion' over a period of 9 minutes post exercise.
End point type	Secondary
End point timeframe:	
Baseline (Week 0) to Week 12	

End point values	EGb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: mL/100 g of tissue				
median (full range (min-max))				
Baseline (Week 0)	166.9 (83.6 to 353)	157.2 (11.8 to 373)		

Week 12	191.6 (86.1 to 417.3)	185.7 (22 to 396.7)		
Change from Baseline (Week 0) to Week 12	-5.2 (-138.2 to 237.4)	0.05 (-156.7 to 212.9)		

Statistical analyses

Statistical analysis title	Perfusion Time Integral
Comparison groups	EGb 761® 120 mg v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9198
Method	Non parametric ANCOVA on the rank test

Secondary: Muscle Reoxygenation Rate Post Exercise.

End point title	Muscle Reoxygenation Rate Post Exercise.
End point description: Muscle reoxygenation rate post exercise was assessed using Myoglobin Hydrogen-1 Nuclear Magnetic Resonance spectroscopy.	
n values for EGb 761 120 mg = 7, 10, 7 and for Placebo = 9, 9 8	
End point type	Secondary
End point timeframe: Baseline (Week 0) to Week 12	

End point values	EGb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: 1/second				
median (full range (min-max))				
Baseline (Week 0)	0.087 (0.035 to 0.156)	0.054 (0.024 to 0.123)		
Week 12	0.058 (0.03 to 0.114)	0.062 (0.021 to 0.087)		
Change from Baseline (Week 0) to Week 12	-0.035 (-0.124 to 0.039)	-0.0035 (-0.058 to 0.049)		

Statistical analyses

Statistical analysis title	Muscle Reoxygenation Rate Post Exercise
Comparison groups	EGb 761® 120 mg v Placebo

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5885
Method	Non parametric ANCOVA on the rank test

Secondary: Muscle Trophicity: Maximum Cross Section of Muscle

End point title	Muscle Trophicity: Maximum Cross Section of Muscle
End point description:	Muscle trophicity measured using Phosphorus 31 Nuclear Magnetic Resonance (P-31 NMR)spectroscopy and calculated based on maximum cross section of muscle (cm ²)
End point type	Secondary
End point timeframe:	Baseline (Week 0) to Week 12

End point values	Egb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: cm ²				
median (full range (min-max))				
Baseline (Week 0)	28.1 (16.6 to 33.1)	28.95 (23.4 to 42.4)		
Week 12	26.8 (16.7 to 33.2)	29.85 (24 to 42.9)		
Change from Baseline (Week 0) to Week 12	0.1 (-1.3 to 0.7)	0.55 (-2.1 to 2.1)		

Statistical analyses

Statistical analysis title	Muscle Trophicity
Statistical analysis description:	Muscle Trophicity - Maximum Cross Section of Muscle
Comparison groups	Egb 761® 120 mg v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.296
Method	Non parametric ANCOVA on the rank test

Secondary: Developed Force During the Exercise Bout

End point title	Developed Force During the Exercise Bout
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End point description:

Developed force during the exercise bout measured using Phosphorus 31 Nuclear Magnetic Resonance (P-31 NMR)spectroscopy

n values for EGb 761 120 mg = 11, 9, 9 and for Placebo = 10, 10, 10

End point type	Secondary
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End point timeframe:

Baseline (Week 0) to Week 12

End point values	EGb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: Joules				
median (full range (min-max))				
Baseline (Week 0)	305.3 (177 to 822.9)	358.1 (207.2 to 1172.8)		
Week 12	277.5 (136.9 to 750.9)	354.35 (200.9 to 1002.1)		
Change from Baseline (Week 0) to Week 12	-32.4 (-146.9 to 56.6)	19.2 (-191.8 to 109.8)		

Statistical analyses

Statistical analysis title	Developed Force during the Exercise Bout
Comparison groups	EGb 761® 120 mg v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3024
Method	Non parametric ANCOVA on the rank test

Secondary: Normalised Work Developed During the Exercise

End point title	Normalised Work Developed During the Exercise
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End point description:

Normalised work developed during the exercise was derived as Work developed during the exercise/([60 X Maximum cross section of muscle]-1100).

Normalised work measured using Phosphorus 31 Nuclear Magnetic Resonance (P-31 NMR)spectroscopy.

n values for EGb 761 120 mg = 11, 9, 9 and for Placebo = 10, 10, 10

End point type	Secondary
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End point timeframe:

Baseline (Week 0) to Week 12

End point values	EGb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: Joules/cm ²				
median (full range (min-max))				
Baseline (Week 0)	12.07 (6.3 to 26)	12 (8.6 to 30.5)		
Week 12	9.23 (7.6 to 24)	11.53 (6.1 to 25.7)		
Change from Baseline (Week 0) to Week 12	-1.03 (-6.3 to 2.6)	0.47 (-4.8 to 4.6)		

Statistical analyses

Statistical analysis title	Normalised Work Developed during the Exercise
Comparison groups	EGb 761® 120 mg v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6641
Method	Non parametric ANCOVA on the rank test

Secondary: Metabolism Efficacy Index

End point title	Metabolism Efficacy Index
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End point description:

The metabolism efficacy index was derived as Normalised work x creatine phosphorylation rate (sec-1). [Normalised work was derived as Work developed during the exercise/(60 X Maximum cross section of muscle-1100)]. Greater values of Metabolism Efficacy index indicate improvement in skeletal muscle energetics while lower values indicate the reverse. Negative values obtained using the formula indicated severe levels of muscle weakness.

n values for EGb 761 120 mg = 11, 9, 9 and for Placebo = 10, 10, 10

End point type	Secondary
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End point timeframe:

Baseline (Week 0) to Week 12

End point values	EGb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: per second				
median (full range (min-max))				
Baseline (Week 0)	0.018 (-0.042 to 0.038)	0.015 (0.01 to 0.029)		
Week 12	0.013 (-0.021 to 0.042)	0.0145 (0.007 to 0.028)		

Change from Baseline (Week 0) to Week 12	0.001 (-0.021 to 0.021)	-0.001 (-0.007 to 0.001)		
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Statistical analyses

Statistical analysis title	Metabolism Efficacy Index
Comparison groups	EGb 761® 120 mg v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1415
Method	Non parametric ANCOVA on the rank test

Secondary: International Cooperative Ataxia Rating Scale [ICARS] (Total Score)

End point title	International Cooperative Ataxia Rating Scale [ICARS] (Total Score)
End point description: The ICARS was used to measure the general clinical symptoms of Friedreich ataxia using four subscales (i.e. Posture and gait disturbances, Kinetic functions, Speech disorders, & Oculomotor disorders). Scores for each subscale quantify the extent of ataxia in each clinically important area and subscale scores are also summed to give a total score ranging from 0 to 100, with 100 indicative of the most severely affected outcome.	
End point type	Secondary
End point timeframe: Baseline (Week 0) to Week 12	

End point values	EGb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: score on a scale				
median (full range (min-max))				
Baseline (Week 0)	35 (21 to 54)	26.5 (20 to 58)		
Week 12	33 (26 to 60)	29 (22 to 54)		
Change from Baseline (Week 0) to Week 12	0 (-9 to 6)	0.5 (-4 to 11)		

Statistical analyses

Statistical analysis title	ICARS - Total Scores
Comparison groups	EGb 761® 120 mg v Placebo

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.728
Method	Non parametric ANCOVA on the rank test

Secondary: ICARS (Posture and Gait Disturbance Score)

End point title	ICARS (Posture and Gait Disturbance Score)
End point description: The ICARS was used to measure the general clinical symptoms of Friedreich ataxia using four subscales including Posture and gait disturbances. Posture and gait disturbances score range from 0 to 34 (Higher scores indicate higher levels of impairment).	
End point type	Secondary
End point timeframe: Baseline (Week 0) to Week 12	

End point values	Egb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: score on a scale				
median (full range (min-max))				
Baseline (Week 0)	19 (8 to 29)	12.5 (7 to 31)		
Week 12	18 (10 to 32)	12 (10 to 29)		
Change from Baseline (Week 0) to Week 12	1 (-6 to 3)	2.8 (-3 to 4)		

Statistical analyses

Statistical analysis title	ICARS (Posture and Gait Disturbance Score)
Comparison groups	Egb 761® 120 mg v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8639
Method	Non parametric ANCOVA on the rank test

Secondary: ICARS (Kinetic Function Score)

End point title	ICARS (Kinetic Function Score)
End point description: The ICARS was used to measure the general clinical symptoms of Friedreich ataxia using four subscales including Kinetic Function. Kinetic Function score range from 0 to 52 (Higher scores indicate higher levels of impairment).	

End point type	Secondary
End point timeframe:	
Baseline (Week 0) to Week 12	

End point values	EGB 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: score on a scale				
median (full range (min-max))				
Baseline (Week 0)	15 (11 to 19)	11.5 (9 to 22)		
Week 12	13 (11 to 24)	13 (11 to 22)		
Change from Baseline (Week 0) to Week 12	0 (-6 to 5)	0.5 (-2 to 5)		

Statistical analyses

Statistical analysis title	ICARS (Kinetic Function Score)
Comparison groups	EGB 761® 120 mg v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.951
Method	Non parametric ANCOVA on the rank test

Secondary: ICARS (Speech Disorders Score)

End point title	ICARS (Speech Disorders Score)
End point description:	
The ICARS was used to measure the general clinical symptoms of Friedreich ataxia using four subscales including Speech Disorders. Speech Disorders Score range from 0 to 8 (Higher scores indicate higher levels of impairment).	
End point type	Secondary
End point timeframe:	
Baseline (Week 0) to Week 12	

End point values	EGB 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: score on a scale				
median (full range (min-max))				
Baseline (Week 0)	2 (0 to 4)	0.5 (0 to 3)		
Week 12	1 (0 to 2)	1 (0 to 2)		

Change from Baseline (Week 0) to Week 12	0 (-3 to 1)	0 (-1 to 2)		
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Statistical analyses

Statistical analysis title	ICARS (Speech Disorders Score)
Comparison groups	EGb 761® 120 mg v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8736
Method	Non parametric ANCOVA on the rank test

Secondary: ICARS (Oculomotor Disorders Score)

End point title	ICARS (Oculomotor Disorders Score)
End point description: The ICARS was used to measure the general clinical symptoms of Friedreich ataxia using four subscales including Oculomotor Disorders. Oculomotor Disorders score range from 0 to 6 (Higher scores indicate higher levels of impairment).	
End point type	Secondary
End point timeframe: Baseline (Week 0) to Week 12	

End point values	EGb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: score on a scale				
median (full range (min-max))				
Baseline (Week 0)	1 (0 to 2)	1.5 (0 to 3)		
Week 12	2 (1 to 3)	2 (1 to 2)		
Change from Baseline (Week 0) to Week 12	0 (0 to 1)	0 (-1 to 2)		

Statistical analyses

Statistical analysis title	ICARS (Oculomotor Disorders Score)
Comparison groups	EGb 761® 120 mg v Placebo

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4005
Method	Non parametric ANCOVA on the rank test

Secondary: Timed 25-foot Walk Test

End point title	Timed 25-foot Walk Test
End point description:	
n values for EGb 761 120 mg = 8, 8, 8 and for Placebo = 8, 8, 8	
End point type	Secondary
End point timeframe:	
Baseline (Week 0) to Week 12	

End point values	EGb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: seconds				
median (full range (min-max))				
Baseline (Week 0)	8.5 (6 to 16)	6.75 (5 to 29.5)		
Week 12	9 (7 to 15.5)	6.75 (5.5 to 29.5)		
Change from Baseline (Week 0) to Week 12	0.5 (-1 to 2)	0 (-2.5 to 0.5)		

Statistical analyses

Statistical analysis title	Timed 25-foot Walk Test
Comparison groups	EGb 761® 120 mg v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0387
Method	Non parametric ANCOVA on the rank test

Secondary: Nine Hole Peg Test (Dominant Hand)

End point title	Nine Hole Peg Test (Dominant Hand)
End point description:	
The nine hole peg test was used to assess cognitive function and in particular, fine motor coordination. The patient was asked to place nine pegs in nine holes and was scored on the amount of time it took to place and remove all nine pegs.	

End point type	Secondary
End point timeframe:	
Baseline (Week 0) to Week 12	

End point values	EGb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: seconds				
median (full range (min-max))				
Baseline (Week 0)	38.5 (31.5 to 71.5)	43.5 (33.5 to 91.5)		
Week 12	42 (29.5 to 86)	40.75 (32 to 89.5)		
Change from Baseline (Week 0) to Week 12	1.5 (-2.5 to 15.5)	-1.5 (-4 to 6.5)		

Statistical analyses

Statistical analysis title	Nine Hole Peg Test (Dominant Hand)
Comparison groups	EGb 761® 120 mg v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2359
Method	Non parametric ANCOVA on the rank test

Secondary: Nine Hole Peg Test (Nondominant Hand)

End point title	Nine Hole Peg Test (Nondominant Hand)
End point description:	
The nine hole peg test was used to assess cognitive function and in particular, fine motor coordination. The patient was asked to place nine pegs in nine holes and was scored on the amount of time it took to place and remove all nine pegs.	
End point type	Secondary
End point timeframe:	
Baseline (Week 0) to Week 12	

End point values	EGb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: seconds				
median (full range (min-max))				
Baseline (Week 0)	47.5 (39.5 to 113)	48.5 (34.5 to 117.5)		
Week 12	53 (36 to 113.5)	46.5 (36.5 to 100.5)		
Change from Baseline (Week 0) to Week 12	0.5 (-11 to 7)	1.75 (-17 to 7)		

Statistical analyses

Statistical analysis title	Nine Hole Peg Test (Nondominant Hand)
Comparison groups	EGb 761® 120 mg v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9681
Method	Non parametric ANCOVA on the rank test

Secondary: Choice Reaction Time Test- Reaction Time

End point title	Choice Reaction Time Test- Reaction Time
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End point description:

The choice reaction time test was used to assess cognitive functioning. On random presentation of one of six signal lights, the patient was asked to respond as quickly and accurately as possible by removing their index finger of the dominant hand from the bottom key and pressing whichever of the top six keys was indicated by the signal. Reaction time was the time elapsed between the presentation of the stimulus and the release of the finger and movement time was defined as the time elapsed between release of the finger and pressure of the second key.

n values for EGb 761 120 mg = 10, 11, 10 and for Placebo = 9, 10, 9

End point type	Secondary
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End point timeframe:

Baseline (Week 0) to Week 12

End point values	EGb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: millisecond				
median (full range (min-max))				
Baseline (Week 0)	513.5 (392 to 1594)	536 (461 to 692)		
Week 12	491 (417 to 899)	531 (446 to 865)		

Change from Baseline (Week 0) to Week 12	8.5 (-1032 to 40)	9 (-89 to 173)		
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Statistical analyses

Statistical analysis title	Choice Reaction Time Test- Reaction Time
Comparison groups	EGb 761® 120 mg v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3607
Method	Non parametric ANCOVA on the rank test

Secondary: Choice Reaction Time Test- Movement Time

End point title	Choice Reaction Time Test- Movement Time
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End point description:

The choice reaction time test was used to assess cognitive functioning. On random presentation of one of six signal lights, the patient was asked to respond as quickly and accurately as possible by removing their index finger of the dominant hand from the bottom key and pressing whichever of the top six keys was indicated by the signal. Reaction time was the time elapsed between the presentation of the stimulus and the release of the finger and movement time was defined as the time elapsed between release of the finger and pressure of the second key.

n values for EGb 761 120 mg = 10, 11, 10 and for Placebo = 9, 10, 9

End point type	Secondary
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End point timeframe:

Baseline (Week 0) to Week 12

End point values	EGb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: millisecond				
median (full range (min-max))				
Baseline (Week 0)	561.5 (344 to 1452)	531 (390 to 986)		
Week 12	555 (406 to 1107)	496.5 (396 to 1419)		
Change from Baseline (Week 0) to Week 12	4.5 (-998 to 190)	-31 (-124 to 433)		

Statistical analyses

Statistical analysis title	Choice Reaction Time Test- Movement Time
Comparison groups	EGb 761® 120 mg v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1683
Method	Non parametric ANCOVA on the rank test

Secondary: Visual Assessment Scale (VAS) of Global Impression - Patient

End point title	Visual Assessment Scale (VAS) of Global Impression - Patient
End point description: The VAS used a 10-cm scoring scale in which values were reported in mm such that 0=bad and 100=good. Total score range on VAS is from 0 to 100.	
End point type	Secondary
End point timeframe: Baseline (Week 0) to Week 12	

End point values	EGb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: mm				
median (full range (min-max))				
Baseline (Week 0)	60 (18 to 80)	68.5 (12 to 100)		
Week 12	67 (12 to 82)	63 (26 to 100)		
Change from Baseline (Week 0) to Week 12	-2 (-47 to 30)	-2 (-20 to 59)		

Statistical analyses

Statistical analysis title	VAS of Global Impression - Patient
Statistical analysis description: Visual Assessment Scale (VAS) of Global Impression - Patient	
Comparison groups	EGb 761® 120 mg v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8415
Method	Non parametric ANCOVA on the rank test

Secondary: Visual Assessment Scale (VAS) of Global Impression - Parents

End point title	Visual Assessment Scale (VAS) of Global Impression - Parents
End point description:	
The VAS used a 10-cm scoring scale in which values were reported in mm such that 0=bad and 100=good. Total score range on VAS is from 0 to 100.	
n values for EGb 761 120 mg = 9, 9, 9 and for Placebo = 9, 9, 9	
End point type	Secondary
End point timeframe:	
Baseline (Week 0) to Week 12	

End point values	EGb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: mm				
median (full range (min-max))				
Baseline (Week 0)	64 (45 to 96)	62 (16 to 87)		
Week 12	64 (31 to 95)	57 (11 to 72)		
Change from Baseline (Week 0) to Week 12	-7 (-14 to 13)	-10 (-25 to 14)		

Statistical analyses

Statistical analysis title	VAS of Global Impression - Parents
Statistical analysis description:	
Visual Assessment Scale (VAS) of Global Impression - Parents	
Comparison groups	Placebo v EGb 761® 120 mg
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1647
Method	Non parametric ANCOVA on the rank test

Secondary: Visual Assessment Scale (VAS) of Global Impression - Investigator

End point title	Visual Assessment Scale (VAS) of Global Impression - Investigator
End point description:	
The VAS used a 10-cm scoring scale in which values were reported in mm such that 0=bad and 100=good. Total score range on VAS is from 0 to 100.	
End point type	Secondary
End point timeframe:	
Baseline (Week 0) to Week 12	

End point values	EGb 761® 120 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: mm				
median (full range (min-max))				
Baseline (Week 0)	78 (67 to 90)	76 (25 to 90)		
Week 12	80 (46 to 87)	74 (46 to 86)		
Change from Baseline (Week 0) to Week 12	-2 (-36 to 13)	-1 (-23 to 52)		

Statistical analyses

Statistical analysis title	VAS of Global Impression - Investigator
Statistical analysis description:	
Visual Assessment Scale (VAS) of Global Impression - Investigator	
Comparison groups	EGb 761® 120 mg v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6265
Method	Non parametric ANCOVA on the rank test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to month 18

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.1
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Reporting groups

Reporting group title	EGb 761® 120 mg
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Reporting group description:

EGb 761 120 mg : EGb 761® 120 mg BID, orally for 12 to 14 weeks

Reporting group title	Placebo
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Reporting group description:

Placebo : Placebo 1 tablet BID, orally for 12 to 14 weeks

Serious adverse events	EGb 761® 120 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 11 (9.09%)	1 / 11 (9.09%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Varicella			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	EGb 761® 120 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 11 (72.73%)	7 / 11 (63.64%)	

Surgical and medical procedures Orthopedic procedure subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 11 (9.09%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all)	3 / 11 (27.27%) 3 1 / 11 (9.09%) 1	2 / 11 (18.18%) 3 0 / 11 (0.00%) 0	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Fall subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1 0 / 11 (0.00%) 0 1 / 11 (9.09%) 1	0 / 11 (0.00%) 0 1 / 11 (9.09%) 1 2 / 11 (18.18%) 2	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2 1 / 11 (9.09%) 2 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0	0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 1 / 11 (9.09%) 1	
Reproductive system and breast disorders			

Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 11 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1 1 / 11 (9.09%) 1	0 / 11 (0.00%) 0 0 / 11 (0.00%) 0	
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Scoliosis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1	1 / 11 (9.09%) 1 0 / 11 (0.00%) 0 0 / 11 (0.00%) 0	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Gastroenteritis viral subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 3 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0	0 / 11 (0.00%) 0 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0 1 / 11 (9.09%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 March 2008	<ul style="list-style-type: none">• Corrections to inconsistencies between the synopsis and body of the protocol• Improvement to the presentation of the selection criteria• Precision to the primary endpoint by adding a PCr depletion threshold for patients at the inclusion visit• Clarification of the NMR contraindication wording: addition of exclusion criteria for patients who did not deplete the PCr pool by more than 40% during the exercise bout and exclusion of patients with implanted iron or magnetic objects• Completion of the ICF
08 July 2008	<ul style="list-style-type: none">• Change to the exclusion criteria such that patients who did not deplete the PCr pool by more than 30% during the exercise bout were excluded whereas previously those who did not deplete the pool by more than 40% were excluded.• Change to the forbidden medications list in the exclusion criteria: deferiprone (Ferriprox®) added• Correction to the number of code break envelope sets• Clarification in the ICF on the change of visit order between the two hospitals• Revision to the Pharmacovigilance and Ipsen contact details
19 February 2009	<ul style="list-style-type: none">• Modification to the Ipsen Pharma BIP contact details• Addition of the "not assessable patient" definition i.e. patients who were considered as noncompliant with the study treatment and/or took forbidden treatment and/or didn't perform the baseline and final assessment of the primary efficacy endpoint• Addition of the replacement patients procedure• Clarification of the primary endpoint to include correction of the rate according to the muscular pH• Correction of the unit for perfusion time integral to mL/100 g of tissue during the first 9 minutes post exercise• Change to the inclusion criteria related to age

07 December 2009	<ul style="list-style-type: none"> • Addition of safety criteria (physical examination and vital signs) • Addition of other muscle improvements in peak post exercise • Deletion of the secondary criteria "post exercise skeletal muscle perfusion" ("peak post exercise perfusion" retained) • Addition of "ataxia history" to the inclusion criteria • Addition of concomitant medication Pioglitazone to the exclusion criteria • The mITT population was defined • Update to statistical section • Modifications to the emergency contact details
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported