Clinical trial results:
Effect of 3-month treatment with F2695 (75mg OD) on improving functional recovery of patients with ischemic stroke. A Multicenter, Randomised, Double-blind, Parallel-group, Placebo-Controlled Study

Summary

EudraCT number	2012-001592-37
Trial protocol	DE ES CZ PT HU BE IT FR SE
Global end of trial date	11 February 2015

Results information

Result version number	v1 (current)
This version publication date	29 November 2018
First version publication date	29 November 2018
Summary attachment (see zip file)	final synopsis F 2695 LP205 (final synopsis F02695 LP 2 05.pdf)

Trial information

Trial identification

Sponsor protocol code	F02695LP205

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pierre Fabre Medicament
Sponsor organisation address	45 place Abel Gance, boulogne, France, 92100
Public contact	Dr Mohammed ZAiM, IRPF – Pierre Fabre Innovation, +33 (0)5-34-50-61-91, mohammed.zaim@pierre-fabre.com
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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	07 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 February 2015
Global end of trial reached?	Yes
Global end of trial date	11 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of 3-month treatment with F2695 (75 mg OD) on improving functional recovery in patients with moderate to severe motor deficits after an ischemic stroke

Protection of trial subjects:

This study was performed in accordance with the principles stated in the Declaration of Helsinki (1964) and subsequent amendments and in accordance with the Good Clinical Practice Guideline (CPMP/ICH/135/95).
The request for authorization by the Competent Authority or its notification (depending on National Regulations) was carried out by the Sponsor.
The screening of patients did not start before the approval of the Ethics Committee was obtained and the study was authorized by the Competent Authority or notified to the Competent Authority (depending on National Regulations).

Background therapy:

During hospitalization in the stroke unit and after discharge, patients were given standard care for stroke patients and had to follow the rehabilitation program recommended by the investigating center. As far as possible, the rehabilitation program was not to change during the study period.

Evidence for comparator:

In the absence of any curative therapy, rehabilitation constitutes the standard mode of therapy to improve functional recovery and quality of life following stroke. Currently, it is recognized that repeated participation by patients in active physical therapeutic programs probably provides direct influence on the process of functional reorganization in the brain and enhances neurologic recovery. A placebo was thus used as a comparator to F2695 in combination with rehabilitation

Actual start date of recruitment	18 June 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	Portugal: 26
Country: Number of subjects enrolled	Spain: 58
Country: Number of subjects enrolled	Sweden: 28
Country: Number of subjects enrolled	Belgium: 29
Country: Number of subjects enrolled	Czech Republic: 71
Country: Number of subjects enrolled	France: 39
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Hungary: 133
Country: Number of subjects enrolled	Italy: 36
Country: Number of subjects enrolled	Russian Federation: 76

Country: Number of subjects enrolled	Switzerland: 13
Worldwide total number of subjects	528
EEA total number of subjects	439

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)	285
From 65 to 84 years	243
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 535 patients with an acute ischemic stroke history within the past 2-10 days were randomized (270 in the F2695 group and 265 in the placebo group), and 528 received the study treatment (267 in the F2695 group and 261 in the placebo group). A total of 113 stroke centers worldwide were initiated of which 87 were active

Pre-assignment

Screening details:

No screening details

Period 1

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

Blinding implementation details:

A randomization list was established by the Clinical Pharmacy Department of the Institut de Recherche Pierre Fabre. This list was computer-generated with validated internal software. The randomization methodology was validated by the Biometry Department (Pierre Fabre Biométrie) before generation. All site personnel were blinded to study treatment assignment. Levomilnacipran (F2695) and placebo were prepared in capsules identical in presentation (brownish red hard capsule size 2).

Arms

Are arms mutually exclusive?	Yes
Arm title	F2695

Arm description:

270 patients were randomised in the F2695 experimental arm for 12 weeks (not including the down taper period)

Arm type	Experimental
Investigational medicinal product name	F02695
Investigational medicinal product code	
Other name	Levomilnacipran
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1. Titration procedure:
The drugs were double-dummy up-titrated in order to reach the target dose on the fifth day. The dose and dosage from Day 1 to Day 5 were:
- Day 1 to Day 2: 25 mg of F2695 OD (1 capsule of 25 mg F2695 and 1 capsule placebo)
- Day 3 to Day 4: 50 mg of F2695 OD (1 capsule of 50 mg F2695 and 1 capsule placebo)
- Day 5 onwards: 75 mg of F2695 OD (1 capsule of 50 mg of F2695 and 1 capsule of 25 mg F2695)

2. Down-taper procedure:
The drugs were double-dummy down-tapered in order to stop the active treatment 10 days after the Week 12 visit. The dose and dosage during the 2 weeks follow-up period were:
- 50 mg of F2695 OD during the next 6 days (1 capsule of 50 mg F2695 and 1 capsule of placebo)
- 25 mg of F2695 OD during the following 4 days (1 capsule of 25 mg F2695 and 1 capsule placebo)

Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

2 capsules of placebo in the morning
- Titration procedure: Up-titration was performed in the stroke unit (acute or post-acute facilities). The drugs were double-dummy up-titrated in order to reach the target dose on the fifth day. The dosage from Day 1 to Day 5 was: 2 placebo capsules (in the morning)
- Down-taper procedure: The drugs were double-dummy down-tapered in order to stop the active treatment 10 days after the Week 12 visit.

The dosage during the 2 weeks follow-up period was 2 placebo capsules (in the morning)

Arm title	placebo

Arm description: -

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

Dosage and administration details:

1. Titration procedure:
The drugs were double-dummy up-titrated in order to reach the target dose on the fifth day. The dose and dosage from Day 1 to Day 5 were:2 capsules a day in the morning

2. Down-taper procedure:
The drugs were double-dummy down-tapered in order to stop the active treatment 10 days after the Week 12 visit. The dosage during the 2 weeks follow-up period was 2 capsules a day in the morning

Number of subjects in period 1	F2695	placebo
Started	267	261
Completed	211	214
Not completed	56	47
Consent withdrawn by subject	20	-
depressive episode	5	7
Adverse event, non-fatal	31	24
other majority of withdrawal	-	14
Lack of efficacy	-	2

Baseline characteristics

Reporting groups	
Reporting group title	F2695
Reporting group description:	
270 patients were randomised in the F2695 experimental arm for 12 weeks (not including the down taper period)	
Reporting group title	placebo
Reporting group description: -	

Reporting group values	F2695	placebo	Total
Number of subjects	267	261	528
Age categorical Units: Subjects			
Adults (18-64 years)	143	142	285
From 65-84 years	124	119	243
85 years and over	0	0	0
Age continuous Units: years			
median	63.0	63.0	
full range (min-max)	37.0 to 81.0	37.0 to 80.0	-
Gender categorical Units: Subjects			
Female	107	104	211
Male	160	157	317
Location of Stroke Units: Subjects			
Lacunar infarct	78	65	143
Total anterior circulation infarct	23	28	51
Partial anterior circulation infarct	132	127	259
Posterior circulation infarct	25	31	56
Other	9	10	19
Body site of hemiparesis or hemiplegia Units: Subjects			
left	170	160	330
right	96	101	197
missing	1	0	1
Mean time from stroke to randomisation Units: days			
arithmetic mean	6.16	5.91	
standard deviation	± 2.42	± 2.40	-

End points

End points reporting groups

Reporting group title	F2695

Reporting group description:

270 patients were randomised in the F2695 experimental arm for 12 weeks (not including the down taper period)

Reporting group title	placebo

Reporting group description: -

Primary: mRS response

End point title	mRS response

End point description:

This global outcomes scale was used to categorize the level of functional recovery in poststroke patients. It is an ordinal, hierarchical scale that assigns patients among 7 global disability levels ranging from 0 (no symptoms) to 5 (severe disability) and 6 (death).
Patients with a mRS ≤ 1 are those who have an excellent recovery. Therefore this criterion is a strong clinically relevant outcome for functional recovery assessment.

End point type	Primary

End point timeframe:

The primary efficacy criterion was the mRS response (yes/no) at Week 12 which was defined as a mRS (ordinal) value of 0 or 1 at Week 12

End point values	F2695	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	267	261		
Units: not applicable				
number (not applicable)	49	36		

Statistical analyses

Statistical analysis title	Full analysis set

Statistical analysis description:

All randomized patients who received at least one dose of the study treatment. The analysis of efficacy and safety was performed on the FAS

Comparison groups	F2695 v placebo
Number of subjects included in analysis	528
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)

Confidence interval	
level	95 %
Variability estimate	Standard deviation
Dispersion value	95

Notes:

[1] - The main statistical objective was to show a difference in the mRS response rate at Week 12 between F2695 75 mg and placebo. Treatment effect on the mRS response was tested using a logistic regression adjusted for the mRS (ordinal) at baseline, recanalization therapy after stroke (yes/no), and the country effect after LOCF imputation of missing data.

[2] - Statistical tests were 2-sided and the significance level was set to 5%.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The time period for adverse events assessment is fourteen weeks (12-week treatment period and 2-week down-titration period).

Adverse event reporting additional description:

At inclusion, any concomitant disease was reported on the eCRF. At each further visit, the occurrence of AEs since the last visit was based on the patient's spontaneous reporting, the Investigator's non-leading questioning and his/her clinical evaluation.
Adverse events were coded by the MedDRA dictionary (Version 17.1)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	F2695

Reporting group description: -

Serious adverse events	Placebo	F2695	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 261 (11.88%)	38 / 267 (14.23%)	
number of deaths (all causes)	6	10	
number of deaths resulting from adverse events	6	10	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to liver			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic neoplasm			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ischaemic limb pain			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arterial occlusive disease			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertension			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cardiac pacemaker insertion			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb amputation			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	2 / 261 (0.77%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Asthenia			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Necrosis			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 261 (0.00%)	4 / 267 (1.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 261 (0.00%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Pulmonary embolism			
subjects affected / exposed	3 / 261 (1.15%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary oedema			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute pulmonary oedema			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Apathy			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Confusional state			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Depression			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder due to a general medical condition			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
feeding tube complication			

subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 261 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	3 / 261 (1.15%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 261 (0.77%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	5 / 261 (1.92%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Carotid artery stenosis			

subjects affected / exposed	1 / 261 (0.38%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic transformation stroke			
subjects affected / exposed	1 / 261 (0.38%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychomotor hyperactivity			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain injury			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery dissection			

subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsions local			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Scintillating scotoma			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 261 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			

subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Hypersensitivity vasculitis			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute prerenal failure			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	5 / 261 (1.92%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 261 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 261 (0.38%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	0 / 261 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Gastroenteritis			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 261 (0.77%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	1 / 261 (0.38%)	0 / 267 (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: 2 %

Non-serious adverse events	Placebo	F2695	
Total subjects affected by non-serious adverse events subjects affected / exposed	184 / 261 (70.50%)	204 / 267 (76.40%)	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	17 / 261 (6.51%) 18	19 / 267 (7.12%) 19	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	15 / 261 (5.75%) 19	13 / 267 (4.87%) 18	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	18 / 261 (6.90%) 21	41 / 267 (15.36%) 43	
Nausea subjects affected / exposed occurrences (all)	10 / 261 (3.83%) 11	21 / 267 (7.87%) 26	
Vomiting subjects affected / exposed occurrences (all)	6 / 261 (2.30%) 6	18 / 267 (6.74%) 22	
Diarrhoea subjects affected / exposed occurrences (all)	15 / 261 (5.75%) 20	9 / 267 (3.37%) 11	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	28 / 261 (10.73%) 29	27 / 267 (10.11%) 30	
Depression subjects affected / exposed occurrences (all)	18 / 261 (6.90%) 19	16 / 267 (5.99%) 17	

Anxiety			
subjects affected / exposed	9 / 261 (3.45%)	15 / 267 (5.62%)	
occurrences (all)	11	16	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	16 / 261 (6.13%)	16 / 267 (5.99%)	
occurrences (all)	16	18	
Pain in extremity			
subjects affected / exposed	16 / 261 (6.13%)	14 / 267 (5.24%)	
occurrences (all)	18	14	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	38 / 261 (14.56%)	41 / 267 (15.36%)	
occurrences (all)	42	50	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 November 2013	Rationale for Amendment Local-A18-PA01-CA01 (Russia) • After admission and discharge from the hospital, patients could have rehabilitation performed at home or in a rehabilitation center. • Some countries initially planned were not participating (Denmark and the Netherlands), so the Russian centers were allowed to recruit more patients: the upper limit of 88 patients was extended to 150 patients. The total number of patients to be included in the study remained at 532.
11 February 2014	This amendment related to the washout duration of the treatments taken before inclusion. Its main objective was to adapt the washout duration of some therapeutic classes to the clinical practice of many study centers in accordance to their local standard of practice. Indeed, the wide washout period (1 month) initially planned in the protocol seemed poorly adapted to the clinical practice of many centers and for some countries not fully adapted to the national guideline of acute stroke phase management regarding some drugs. In order to help the investigators to include a representative sample of the population treated in their stroke unit, Pierre Fabre clarified the requested washout windows of drugs usually used in many sites during the acute phase of stroke.
01 July 2014	The main purpose of the current amendment is to switch the response range from ≤ 2 to ≤ 1 and thus use a "hard clinical endpoint" by restricting the patient response definition to those who have an excellent functional outcome with a mRS score of 0 or 1 (no significant disability or no disability). The rationale for this change is based on methodological and clinical considerations. A switch from phase 2 to phase 3 of the clinical study phase was implemented.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported