F02695 LP 2 05

CLINICAL STUDY REPORT

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

Investigational product: Levomilnacipran/prolonged-release hard capsules

Study Design: Multicenter, Randomized, Double-blind, Parallel-group, Placebo-Controlled

EudraCT number: 2012-001592-37

Protocol number: F02695 LP 2 05

Phase of development: III

Date of first enrolment: 25 September 2012

Date of last completed: 11 February 2015

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Date of report: 07 December 2015

Study performed in compliance with Good Clinical Practice.

1 SYNOPSIS

Name of Sponsor/Company *Pierre Fabre Médicament* represented by the *Institut de Recherche Pierre Fabre* (*IRPF*)	Name of Finished Product Levomilnacipran	Name of Active Ingredient F2695 prolonged-release
Protocol Number: F02695 LP 2 05		
Title of Study: Effect of 3-month treatment with F2695 (75 mg once daily [OD]) on improving functional recovery of patients with ischemic stroke. A Multicenter, Randomized, Double-blind, Parallel-group, Placebo-Controlled Study. The LIFE Study		
Investigators and Study Centers: A total of 113 stroke centers worldwide (of which 87 were active) including Belgium (n = 9, of which 7 were active), Czech Republic (n = 9, of which 6 were active), France (n = 13, of which 9 were active), Germany (n = 14, of which 10 were active), Hungary (n = 11, all sites were active), Italy (n = 9, of which 6 were active), Portugal (n = 7, of which 5 were active), Russia (n = 16, of which 13 were active), Spain (n = 13, of which 11 were active), Sweden (n = 8, of which 6 were active), and Switzerland (n = 4, of which 3 were active).		
Publication (reference): Not applicable		
Study Period (years): 3 years Date of First Enrollment: 25 September 2012 Date of Last Completed: 11 February 2015	Phase of Development: III	

Objectives:

The primary objective of this study was to assess the effect of 3-month treatment with F2695 (75 mg once a day [OD]) on improving functional recovery in patients with moderate to severe motor deficits after an ischemic stroke.

The secondary objectives of this study were:

- To assess the effect of F2695 on:
  - Motor recovery.
  - Occurrence and recurrence of depression.
- To evaluate the safety and tolerability of F2695 in patients with ischemic stroke.

Methodology: This phase III trial was conducted as a worldwide multicenter, randomized, double-blind, parallel-group, placebo-controlled study in patients admitted to a stroke unit after an ischemic stroke. A total of 532 patients aged between 18 and 80 years, who had had an acute ischemic stroke within the previous 2 to 10 days and had not recovered, were planned to be randomized (266 in each treatment group).

The study lasted 14 weeks including 12 weeks of double-blind treatment followed up by a further 2-week double-blind down-taper period. Seven visits were scheduled: Inclusion (baseline), Week 2, Week 4, Week 7, Week 10, Week 12 (End-of-treatment evaluation) and Week 14 (End-of-study visit).

Patients received the standard care management of stroke including an active rehabilitation program. At the inclusion/randomization visit, eligible patients were randomly assigned (1:1) to 1 of 2 parallel treatment groups: placebo or F2695 75 mg OD. The randomization was centralized via an interactive response technology. Randomization was pre-stratified by country according to the modified Rankin Scale (mRS) value at inclusion (mRS score of 4 versus 5) and the recanalization therapy after stroke (yes/no). The study treatment was taken once daily (2 capsules). The starting dose for patients randomized to the F2695 group was 25 mg OD. Patients were double-dummy up-titrated in order to reach the target dose (75 mg/day) on the fifth day. The up-titration was performed in the stroke unit (acute or post-acute facilities) under the supervision of the Investigator's team. During hospitalization in the stroke unit and after discharge, patients were given the standard care for stroke and were required to follow the rehabilitation program recommended by the investigating center.

The main efficacy outcome measures on functional recovery (mRS), motor recovery (National Institutes of Health Stroke Scale [NIHSS] motor scale), and depression (Montgomery-Åsberg Depression Rating Scale [MADRS] and/or Clinical Global Impression – Severity Scale in Depression [CGI-Depression]) were obtained at each visit.

Number of Patients (planned and analyzed): Five hundred thirty-two patients were planned to be randomized. A total of 535 patients at 87 sites were randomized and 528 patients were treated (267 in the F2695 group; 261 in the placebo group).

Diagnosis and Main Criteria for Inclusion:

Key inclusion criteria:

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In order to be considered eligible for inclusion into study, patients admitted to stroke units were required to fulfil all of the following criteria:

- Male or female patients, 18 to 80 years of age, inclusive
- Had a confirmed acute ischemic stroke within the previous 2-10 days , associated with:
  - Unilateral motor deficit (hemiparesis or hemiplegia)
  - NIHSS Motor score ≥ 5
  - mRS score of 4 or 5
- Able and willing to comply with the site rehabilitation program requirements,
- Signed written informed consent.

Test Product, Dose and Mode of Administration, Batch Number:
The test product (F2695 75 mg) was administered OD in 2 capsules (25 mg and 50 mg). Patients had to swallow 2 capsules of the study drug with a glass of tap water OD in the morning during a meal.
Batch numbers:
CFS 263 – CFS 262 (PC20120403 – expiry date 02/2015) – treatment unit 1001 to 1060
CFS 263 – CFS 262 (PC20120506 – expiry date 02/2015) – treatment unit 1061 to 1260
CFS 263 – CFS 262 (PC20120701 – expiry date 02/2015) – treatment unit 1261 to 1510
CFS 263 – CFS 262 –CL0017 C1 – CL0017 C2 (PC20121115 – expiry date 02/2015) – treatment unit 1511 to 1710
CL0017 C1 – CL0017 C2 (PC20121203 – expiry date 02/2015) – treatment unit 1711 to 1794
CL0034 B1 – CL0034 B2 (PC20130504 – expiry date 01/2016) – treatment unit 1795 to 2034
CL0034 B1 – CL0034 B2 (PC20130611 – expiry date 03/2016) – treatment unit 2035 to 2302

Duration of Treatment: 14 weeks: 12 weeks (including 4 days up-titration) + 2 weeks (tapering)

Reference Therapy, Dose and Mode of Administration, Batch Number: Identical placebo capsules
Batch numbers:
CFS 259 (PC20120403 – expiry date 02/2015) – treatment unit 1001 to 1060
CFS 259 (PC20120506 – expiry date 02/2015) – treatment unit 1061 to 1260
CFS 259 (PC20120701 – expiry date 02/2015) – treatment unit 1261 to 1510
CFS 259 (PC20121115 – expiry date 02/2015) – treatment unit 1511 to 1710
CFS 259 (PC20121203 – expiry date 02/2015) – treatment unit 1711 to 1794
CL0035 (PC20130504 – expiry date 01/2016) – treatment unit 1795 to 2034
CL0035 (PC20130611 – expiry date 03/2016) – treatment unit 2035 to 2302

Endpoints for Evaluation:
Efficacy:
Primary Analyses:
The primary criterion was the mRS response (yes/no) at Week 12, defined as an mRS (ordinal) score of 0 or 1 at Week 12.
Secondary Analyses:
The secondary efficacy endpoints were:

- mRS response at Week 12 defined as mRS ≤ 2 at Week 12
- Time to first sustained mRS ≤ 2 up to Week 12
- Change in mRS (ordinal) at Week 12
- mRS score value (ordinal) at Week 12
- NIHSS response defined as NIHSS Total score ≤ 1 at Week 12
- Change from baseline in NIHSS Total score (continuous) to Week 12
- Change in NIHSS Motor score (continuous) at Week 12
- Change in NIHSS Language score (continuous) to Week 12
- Composite response at Week 12 based on mRS, and NIHSS Total and Motor scores at Week 12 defined as mRS ≤ 2 and NIHSS Total score ≤ 5 and NIHSS Motor score ≤ 2
- CGI-Depression score (continuous) at Week 12
- MADRS Total score (continuous) at Week 12
- Depressive episode (yes/no) up to Week 12 defined as MADRS ≥ 26 and/or CGI-Depression ≥ 5 after last observation carried forward (LOCF) imputation of missing data
- Time (Day) to end of the in-hospital period (acute or post-acute facilities)

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Safety:

The evaluated safety variables were:

- Concomitant treatments
- Adverse events (AE), treatment-emergent AEs (TEAEs), deaths, serious adverse events (SAEs) and significant AEs (AEs that led to discontinuation from the study)
- Physical examination
- Vital sign measurements
- Electrocardiograms
- Clinical laboratory values
- Heart rate (HR) according to mRS response (≤ 1) at Week 12

Statistical Methods:

Analysis Populations:

- **The Randomized Patients Set** consisted of all patients who signed an informed consent and were allocated treatment with Interactive Voice and Web Response System®.
- **The Full Analysis Set** (FAS) consisted of all randomized patients who received at least one dose of the study treatment. The analysis of efficacy and safety was performed on the FAS.
- **The Per-Protocol Set** consisted of all FAS patients who did not have any major protocol deviation.
- **The 3-Month mRS Assessable Patient Set** consisted of all patients in the FAS who had a non-missing mRS value at the Week 12 visit regardless of whether patient prematurely discontinued the study treatment during the 12-week double-blind study treatment period or not.
- **The 3-Month mRS Assessable Treated Completer Patient Set** consisted of all patients in the FAS who had a non-missing mRS value at the Week 12 visit and completed the 12-week double-blind study treatment period as per investigator's judgment.

Primary Efficacy Criterion: The primary efficacy criterion was the mRS response (yes/no), defined as a mRS (ordinal) score of 0 or 1 at Week 12.

Main analysis: Comparison of mRS response rate at Week 12 between F2695 75 mg and placebo using a logistic regression adjusted for the mRS score (ordinal) at baseline, recanalization therapy after stroke (yes/no), treatment effect, and the country effect after LOCF imputation of missing data.

Sensitivity analyses:

- Comparison of mRS response rate at Week 12 between F2695 75 mg and placebo using pooled logistic regressions adjusted for the mRS score (ordinal) at baseline, recanalization therapy after stroke (yes/no), treatment effect, and the country effect after multiple imputation of missing data

- main analysis repeated except that the outcome values of patients prematurely withdrawn from study treatment reported up or equal to the scheduled visit after study treatment discontinuation were considered in this analysis. The other visits, if any, will be removed.

- main analysis repeated but with NIHSS Total score categorized into 2 classes (< 10 and ≥ 10), and age categorized into 2 classes < 65 and ≥ 65 years as explicative factors in the model.

Additional Analyses:

- Primary analysis of the main criterion conducted on the subgroups of patients:
  - mRS at baseline 4 versus 5 (for this subgroup analysis, mRS at baseline was removed from the model)
  - Recanalization therapy (thrombolysis) after stroke (yes versus no) (for this subgroup analysis, recanalization therapy factor was removed from the model).
  - Age < 65 versus ≥ 65 years
  - Previous stroke occurrence (yes versus no)
  - NIHSS Total score < 10 versus ≥ 10
  - NIHSS Motor score ≤ 6 versus 7-8 versus ≥ 9
  - Location of stroke lacunar infarct versus the others (non-lacunar infarct)
- Primary analysis of the main criterion on the Per-Protocol Set
- Primary analysis of the main criterion on the 3-Month mRS Assessable Patient Set
- Primary analysis of the main criterion on the 3-Month mRS Assessable Treated Completer Patient Set

Secondary Efficacy Criteria:

- mRS response defined as mRS 0, 1, or 2 at Week 12

Same analysis as the primary analysis of the primary efficacy criterion.

- Time to first sustained mRS (≤ 2) up to Week 12

Comparison between treatment groups using the Gehan test and description using survival curves according to the Kaplan Meier method (see section 14.2 of the SAP).

- Change in mRS (ordinal) at Week 12

Comparison between treatment groups using:
-an exact logistic regression (proportional odds model) adjusted for the mRS (ordinal) at baseline, recanalization therapy after stroke (yes/no), and the country effect after LOCF imputation of missing values.
-same analysis model as above combined with multiple imputation. - the Cochran-Mantel-Haenszel statistics (row mean scores) stratified by the mRS (ordinal) at baseline, recanalization therapy after stroke (yes/no), and the country effect, using modified ridit scores.

- mRS score value (ordinal) at Week 12

Same analysis as the change in mRS (ordinal) to Week 12

- NIHSS response defined as NIHSS Total score ≤ 1 at Week 12

Comparison between treatment groups using a logistic regression model adjusted for the NIHSS (continuous) at baseline, the mRS (ordinal) at baseline, recanalization therapy after stroke (yes/no), and the country effect after LOCF imputation of missing data.

- Change from baseline in NIHSS Total score (continuous) at Week 12.

Comparison between treatment groups using covariance analysis model adjusted for the NIHSS Total score (continuous) at baseline, the mRS (ordinal) at baseline, recanalization therapy after stroke (yes/no), and the country effect after LOCF imputation of missing data.

- Change in NIHSS Motor score (continuous) at Week 12

Comparison between treatment groups using covariance analysis model adjusted for the NIHSS Motor (continuous) at baseline, the mRS (ordinal) at baseline, recanalization therapy after stroke (yes/no), and the country effect after LOCF imputation of missing data.

- Change in NIHSS Language score (continuous) to Week 12

Comparison between treatment groups using covariance analysis model adjusted for the NIHSS Language (continuous) at baseline, the mRS (ordinal) at baseline, recanalization therapy after stroke (yes/no), and the country effect after LOCF imputation of missing data.

- Composite response at Week 12 based on mRS, and NIHSS Total and Motor scores at Week 12, defined as mRS score ≤ 2, NIHSS Total score ≤ 5, and NIHSS Motor score ≤ 2.

Comparison between treatment groups after LOCF imputation of missing data using a logistic regression model adjusted for the NIHSS Total and Motor scores (continuous) at baseline, the mRS (ordinal) at baseline, recanalization therapy after stroke (yes/no), and the country effect.

- CGI-Depression score (continuous) at Week 12.

Comparison between treatment groups after LOCF imputation of missing data using covariance analysis model adjusted for CGI-Depression (continuous) at baseline, mRS (ordinal) at baseline, recanalization therapy after stroke (yes/no), and the country effect.

- MADRS Total score (continuous) at Week 12.

Comparison between treatment groups after LOCF imputation of missing data using covariance analysis model adjusted for the MADRS Total score at baseline, the mRS (ordinal) at baseline, recanalization therapy after stroke (yes/no), and the country effect.

- Depressive episode (yes/no) up to Week 12, defined as MADRS ≥ 26 and/or CGI-Depression ≥ 5 after LOCF imputation of missing data

Comparison between treatment groups using logistic regression analysis adjusted for CGI-Depression at baseline, the mRS (ordinal) at baseline, recanalization therapy after stroke (yes/no), and the country effect, if relevant (at least 5% depressive episodes).

- Time (Day) to end of the in-hospital period (acute or post-acute facilities)

Comparison between treatment groups using the Gehan test and description using survival curves according to the Kaplan Meier method.

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- Other criteria:

The statistical analyses (logistic regression for qualitative criteria and analysis of covariance for quantitative criteria using LOCF imputation) planned for the efficacy criteria (mRS response ≤ 1, mRS response ≤ 2, change in mRS score, mRS score value, NIHSS response, change in NIHSS Total score, change in NIHSS Motor score, change in NIHSS Language score) at the visit Week 12 was re-performed at the other visits for descriptive purpose only.. The analysis of the efficacy criteria at the visit Week 14 (using LOCF method) was done for the 3-month mRS Assessable Treated Completer Patient Set. Only LOCF method was performed for the analysis at Week 14 (no multiple imputation was used).

Safety Analysis:

AEs:

-N (%) of patients: with ≥ 1: treatment-emergent AE, serious AE (SAE), AE leading to study treatment discontinuation, AE leading to withdrawal from the study, treatment-related AE (suspected to be related or insufficient causality data), ≥ 1 SAE

- The number and percentage of patients with ≥ 1 AE by system organ class, preferred term and treatment group.

-The number and percentage of patients with ≥ 1 treatment-related AE by preferred term and treatment group

-The number and percentage of patients with at least one AE by SOC, preferred term, treatment group, maximum intensity, the most severe relationship to the study drug, and the minimal onset time

-Tabulated individual data for Deaths, SAEs and for AEs leading to definitive study treatment discontinuation or change in dose

Clinical Laboratory:

- Descriptive statistics for values and changes over time,
- N (%) of patients with: 1) predefined potentially clinically significant change (PSC); 2) PSC leading to potentially clinically significant out-of-range value (PSCV)
- N (%) of patients with variations at each assessment time as compared with the baseline values by treatment group using the 3-point scale (low, normal, high)
- Scatter plots as a function of baseline values for last values
- Tabulated individual data for clinically noteworthy abnormal lab values (CNALV)

Vital Signs:

- Descriptive statistics for values and changes over time,
- N (%) of patients with: 1) predefined PSC; 2) PSC leading to predefined PSCV;
- N (%) of patients with changes from baseline to max. (and min.) post-baseline value
- N (%) of patients with episode of orthostatic hypotension observed on treatment

Electrocardiogram: Values and changes from baseline over time for RR, HR, PR, QRS, QT, and QTc intervals. Analyses of QTcB and QTcF intervals and changes from baseline and description of electrocardiogram abnormalities reported.

Heart Rate according to mRS response (≤ 1) at Week 12: Descriptive statistics of values and changes from baseline of supine HR (bpm) at Week 12 using LOCF imputation by treatment group on the subgroups of patients with mRS response (≤ 1) at Week 12 versus non-mRS response at Week 12.

Patient Disposition: A total of 535 patients were randomized (270 patients in the F2695 group and 265 patients in the placebo group). The number of patients in each analysis group was as follows (F2695; placebo): FAS (267; 261), Per-Protocol Set (223; 222), 3-Month mRS Evaluable Patients Set (238; 238), and the 3-Month mRS Evaluable and Treatment Completers Patients Set (210; 214).

Key Demographics: No imbalance between treatment groups was detected at baseline with regard to demographic variables and stroke characteristics. Overall 60% of the patients were male and 40% were female. The mean age was 63.1 years in the F2695 group and 62.7 years in the placebo group. Lacunar infarct was reported for 27.1% of patients overall (29.2% in the F2695 group and 24.9% in the placebo group). The mean time from stroke to randomization was 6.16 days in the F2695 group and 5.91 days in the placebo group. Most patients did not have recanalization therapy after the stroke (75.3% in the F2695 group and 75.1% in the placebo group). Of the 10.9% of subjects in the F2695 group and 13.4% in the placebo group

who had a history of stroke, most had a previous ischemic stroke (89.7% and 91.4% of patients in the F2695 and placebo groups, respectively). Overall, 444 of 528 patients (84.1%) had concomitant hypertension (83.5% in the F2695 group and 84.7% in the placebo group) and 152 of 528 patients (28.8%) had either type 1 or 2 diabetes (89 of 267 patients [33.3%] in the F2695 group and 63 of 261 patients [24.1%] in the placebo group). Some form of dyslipidemia was reported by 52.1% of the patients (275 of 528): 50.9% in the F2695 group and 53.3% in the placebo group.

Summary of Results:

Efficacy:

Primary efficacy

- At week 12, 18.4% of patients in the F2695 group and 13.8% in the placebo group had an mRS response, defined as an mRS score of 0 or 1; the difference was not statistically significant (p = 0.0944, OR=1.53).
- For the FAS, there was no statistically significant difference between treatment groups with regard to the Week 12 mRS response (≤ 1) based on baseline mRS score (4 vs 5), recanalization therapy after stroke (yes vs no), age (< 65 vs ≥ 65 years), previous stroke occurrence (yes vs no), baseline NIHSS Total score (< 10 vs ≥ 10), baseline NIHSS Motor score ≤ 6 vs 7-8 vs ≥ 9), or location of stroke (lacunar vs other). A trend in favor of F2695 was observed for the following subgroups: baseline mRS score=4 (OR=1.60), age < 65 years (OR=1.81), other than lacunar strokes (OR=1.58), recanalization therapy after stroke (OR=2.24), pervious stroke (OR=6.51), NIHSS Total score < 10 (OR=1.64) and baseline NIHSS Motor score ≤ 6 (OR=1.5).
- None of the analyses exhibited statistically significant differences between treatment groups.

Secondary efficacy

Domain	**Variable**	**% Responders at Week 12 (LOCF); Odds Ratio estimate; P-Value Or Odds Ratio Estimate at Week 12 (LOCF); P-Value Or Mean (SE) Adjusted Change at Week 12 (LOCF); P-Value Or Gehan Test P-Value**	
		Placebo n=261	**F2695 n=267**
mRS	**% of mRS responders (score ≤ 1)**	**13.8%**	**18.4%; OR=1.5311; p=0.0944**
	% of mRS responders (score ≤ 2)	42.5%	42.3%; OR=1.0294; p=0.8801
	Time to first sustained mRS score ≤ 2		p=0.72
	Change in mRS score (ordinal)		OR=0.9613 ; p=0.8010
	mRS score ordinal		OR=0.9676 ; p=0.8340
NIHSS	% of NIHSS responders	16.9%	19.5%; OR=1.3295; p=0.2560
	NIHSS Total Score	-5.0 (0.2)	-5.0 (0.2) ; p=0.9869
	NIHSS Motor Score	-3.6 (0.1)	-3.7 (0.1) ; p=0.5652
	NIHSS Language Score	-0.5 (0.0)	-0.5 (0.0) ; p=0.7368
Composite criterion	Composite response (mRS ≤ 2, NIHSS Total score ≤ 5, and NIHSS motor score ≤ 2)	32.6%	34.8%; OR=1.2478; p=0.3205
Depression	CGI-Depression score	0.0 (0.0)	0.1 (0.0) ; p=0.7948
	MADRS score	-1.9 (0.3)	-1.2 (0.3) ; p=0.0887
	% Post-baseline depressive episode (MADRS Total score ≥ 26 and/or a CGI Depression score ≥ 5)	1.5%	3.0% ; N/A
Discharge	Time to discharge from randomization date		p=0.84
	Time to discharge from admission date		p=0.72

Safety Results:

- Exposure to the study drug: the mean number of days of exposure to the study drug was 83.4 days in the F2695 group and 85.5 days in the placebo group. The median exposure was 98.0 days for both groups.
- All AEs were treatment-emergent except for 1 event in 1 patient in each treatment group. Most patients had ≥ 1 AE reported: 204 of 267 patients (76.4%) in the F2695 group and 184 of 261 (70.5%) in the placebo group.
- In the F2695 group, 19.9% of patients and 13% of patients in the placebo group had ≥ 1 study drug-related (as determined by the investigator) TEAE.

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• Two SOCs corresponding to reported AEs had ≥ 5 percentage point difference between treatment groups (F2695; placebo): gastrointestinal disorders (86 patients [32.2%]; 54 patients [20.7%]) and cardiac disorders (45 patients [16.9%]; 24 patients [9.2%]). • Sixty-nine patients had 109 treatment-emergent SAEs during the study (38 (14.2%)in the F2695 group and 31 (11.9%) in the placebo group), most of which were moderate or severe. • Sixteen patients (10 in the F2695 group and 6 in the placebo group) died during the study, but none of the fatal events was suspected to be related to the study treatment. • Seventy-one patients had AEs that led to permanent discontinuation of the study drug (40 [15%] in the F2695 group and 31 [11.9%] in the placebo group).		
Conclusions: Treatment with F2695 over 12 weeks did not result in statistically significant differences compared with placebo in any of the analyses of the primary or secondary efficacy criteria in patients with ischemic stroke. Patients in both treatment groups improved at similar rates throughout the study. Overall, the study drug was well tolerated and AEs occurred at similar rates between treatment groups.		
Date of the Report: 02 December 2015		