Pierre Fabre Médicament
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1. TITLE PAGE

ABRIDGED CLINICAL STUDY REPORT

Study of the analgesic effects of repeated doses of F13640 in spinal cord injury patients with moderate to severe central neuropathic pain

Investigational product:	F13640 (capsules 0.5 mg).
Study Design:	A multinational, multicentre, randomized, double blind, parallel groups, placebo-controlled study
Protocol Number:	F13640 GE210
Eudract CT Number	2007-003230-42
Phase of Development:	II
Date of First Enrolment:	February 19, 2008.
Date of Last Completed:	December 03, 2008.
Co-ordinator:	**Dr Nadine ATTAL** Hôpital Ambroise Paré - 9 Avenue Charles de Gaulle, F-92104 Boulogne Cedex France - Phone +33 (0) 149 095 946.
Sponsor Representatives for study report:	Clinical Trial Director M.-T. Pétrissans, +33 (0) 562 242 757. Pharmacokinetic Study Manager L. Barthe, +33 (0) 562 245 441. Project Statistician S. Roye PFB, Phone +33 (0) 562 242 749). Medical Writer C. Touzet, +33 (0) 562 242 736.
Date of report:	**May 18, 2010**

Study performed in compliance with Good Clinical Practice.

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2. SYNOPSIS

Name of Company: Pierre Fabre Médicaments	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product:	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)***:**	**Vol.: .....Page: .....**	

Title of study	**Study of the analgesic effects of repeated doses of F13640 in spinal cord injury patients with moderate to severe central neuropathic pain.**	
International Coordinating Investigator:	Dr Nadine ATTAL Hôpital Ambroise Paré 9 Avenue Charles de Gaulle, F-92104 Boulogne Cedex.	
Investigators:	24 investigators (24 neurology and rehabilitation centres) in 7 countries Belgium, Finland, France, Hungary, Italia, Netherlands and Spain.	
Study centres	24 centres recruited.	
Publication (reference)	Not applicable.	
Studied period:		**Phase of development: II.**
date of first enrolment:	February 19, 2008.	
date of last completed:	December 03, 2008.	
Objectives:	Primary: to evaluate the efficacy of F13640 (1 mg *b.i.d.*) in spinal cord injury patients suffering from moderate to severe central neuropathic pain.. Secondary: The secondary objectives were to evaluate the pain relief, the impact on sleep, mood and motricity, the safety and the tolerability of F13640 in spinal cord injury patients suffering from moderate to severe central neuropathic pain. Consecutively to the sponsor's decision of premature end of the study due to strategic reason, the primary objective was not reached and only the parameters of pain relief, patient global impression of change, safety and tolerability of F13640 were analysed.	
Methodology:	Study design: international, multicentre, 12-week, randomised, double-blind, placebo-controlled, parallel groups design. Treatment schedule: on Day 1, patients received 0.5 $mg.day^{-1}$ of F13640 or placebo for 2 days. If the patients tolerated this dose, they were stepped up to a daily dose of 1 $mg.day^{-1}$ of F13640 (or placebo) for 2 days, 1.5 $mg.day^{-1}$ of F13640 (or placebo) for 2 days and 2 $mg.day^{-1}$ of F13640 (or placebo) from Day 7 to Day 84.	
Number of patients (planned and analysed):	124 patients were planned. From the 68 selected patients, 45 were randomised and treated (25 on placebo and 20 on F13640).	
Diagnosis and main criteria for inclusion:	– Patients having signed the written informed consent or their oral informed consent attested by a witness independent of the investigator and of the sponsor, in case of motor function impairment in the arms, – Male or female out patients or institutionalized patients, aged from 18 years to 65 years (both included), – Diagnosis of spinal cord injury (post-traumatic, post-ischemic, non progressive myelitis, syringomyelia) for at least 1 year before the selection, with stable neurological lesions for at least 6 months before the selection, – Diagnosis of central neuropathic pain due to spinal cord injury, based on clinical history, clinical examination and appropriate assessment of patient's signs and symptoms, according to the International Association for the Study of Pain definition,	

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Test product, Dose, Mode of administration, Batch number:	F13640 (0.5 mg) capsules 2 mg.day^{-1} for oral route.		
	F13640 capsules 0.5 mg:	Batch: CFS172	expiry date: December 2008.
	F13640 capsules 0.5 mg:	Batch: CFS197	expiry date: September 2009.
Duration of treatment	12 weeks including a 7-day up-titration period.		
Reference therapy, Dose, Mode of administration, Batch number	Placebo capsules for oral route.		
	Placebo capsules	Batch: CFS171	expiry date: June 2011.
	Placebo capsules	Batch: CFS182	expiry date: October 2011.

Criteria for evaluation

- Weekly 24-hour recall pain intensity score, paroxysmal pain and amount of rescue medication (including prohibited analgesics), antispastic or anticonvulsant concomitant treatments every day from the day following selection visit to Day 94.
- Patient Global Impression of Change on Day 84.
- Brush evoked allodynia test at each visit from selection visit to Day 94.
- Score of pain relief, Brief Pain Inventory-short form, Neuropathic Pain Symptom Inventory on Day 1 (baseline), Day 28 and Day 84.
- Pharmacokinetic assessment on Day 28, Day 56 and Day 84.
- Adverse events at each visit from Day 1 to Day 94.
- Laboratory parameters (haematology, biochemistry) at the selection visit, at each visit from Day 28 to Day 94.
- Vital signs, physical findings, concomitant treatments at each visit from selection visit to Day 94.
- ECG at selection visit, on Day 84 and Day 94.

The following efficacy parameters (Medical Outcomes Study-Sleep scale, Hospital Anxiety and Depression Scale, Modified Ashworth scale, Mayo Clinic scale, Walking Index for Spinal Cord Injury II, Penn scale, Spinal cord independence measure, International index of erectile function, Hoffmann-reflex (H-reflex) of the soleus muscle) were not analysed.

Statistical methods

Descriptive statistics for demographic characteristics, efficacy and safety data.

Pharmacokinetics:

Measured concentrations of F13640 were tabulated and plotted versus actual sampling times relative to the time of the last administration.

Summary - Conclusions:

In regard to the context of this study, the number of randomised and treated patients was lower than planned. No validation committee was performed, no determination of major protocol deviations was carried out. The disposition of the 45 randomised treated patients was the following

	placebo	**F13640**
randomised treated	25	20
premature end due to sponsor's decision	8	6
completers	9	7

The studied population, aged 48.7 (sd = 11.4) years on average was mainly composed of men (32/45, *i.e.* 71.1%), respectively 19/25 on placebo and 13/20 on F13640. The 45 randomised treated patients suffered from spinal cord injury for about 7 years. This cord injury was mainly post traumatic in 35/45 patients (19/25 on placebo, 16/20 on F13640). They suffered from moderate or severe central neuropathic pain for about 7 years in patients on placebo and about 6 years in patients on F13640.

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Efficacy results

No clinically relevant difference was observed between treatment groups and did not allow to conclude whether F13640 has any therapeutic effect in this population. The majority of patients from both treatment groups reached the dosage of 1 mg *b.i.d.* from Day 7, respectively 22/25 patients on placebo and 13/20 patients on F13640.

Results from baseline to Day 84 (LOCF approach)	n** patients Placebo vs F13640	Placebo N* = 25	F13640 N* = 20
Change in the weekly 24-hour recall pain intensity score	24 vs 20	-0.01 (sd = 1.50)	-0.54 (sd = 1.39)
Change in the weekly 24-hour paroxysmal pain	24 vs 20	-0.32 (sd = 1.22)	-0.68 (sd = 1.42)
Results from baseline to Day 84 (OC approach)		-	-
Change in the weekly average 24-hour recall pain intensity score	10 vs 7	-0.45 (sd = 1.71)	-0.67 (sd = 1.90)
Change in the weekly average 24-hour paroxysmal pain	10 vs 6	-0.92 (sd = 1.63)	-1.12 (sd = 2.26)
Change in score of pain relief	9 vs 8	-4.4 (sd = 28.8)	+3.8 (sd = 17.7)

*) **N = number of patients in each treatment group per data set.**
) **n = number of patients in each treatment group with available data.

Pharmacokinetic results

Overall, 31 plasma concentrations of F13640 with appropriate administration date and time, sampling date and time, and dosing records were used to perform the descriptive analysis. Plasma concentrations observed from theoretical Day 28 to Day 84 ranged from 0.239 to 100 $ng.mL^{-1}$ after administration of 0.5 mg od (relative time interval from the last drug intake = 11.5 to 87.7 hours), and from BLOQ to 122 $ng.mL^{-1}$ after 1 mg *b.i.d.* (relative time interval = 0.17 to 12.5 hours).

Safety results

Overall, 71 TEAE were reported, 33 in 12/25 patients on placebo and 38 in 13/22 patients on F13640. Among them, 23/33 TEAE on placebo and 24/38 on F13640 were considered by the Investigator as drug related (not excluded or unassessable). The most commonly observed drug related TEAE on F13640 (*i.e.* in ≥ 3/22 patients) were dizziness (4/22 patients) and headache (3/22 patients). These drug related TEAE occurred mainly during the up-titration period, were mainly of mild or moderate intensity and resolved spontaneously. Two (2) TEAE in 2 patients on placebo (hypokalaemia, pain) and 6 TEAE in 6 patients on F13640 (haemangioma, gastro-intestinal disorder, muscle spasticity, asthenia, dyspepsia, pyelonephritis) led to premature study discontinuation. Among the 5 SAE notified in 5 patients on study treatment (3 on placebo, 2 on F13640), only pyelonephritis on F13640 was considered by the Investigator as drug related, but not by the sponsor, and was observed in a patient with a history of urinary tract infection and resolved within 15 days on curative treatment.

No clinically relevant abnormalities were observed in laboratory data, vital signs, in particular haemodynamic parameters, or electrocardiograms.

The most common TEAE, considered as drug related by the Investigator (> 1 patient in either group) by decreasing order in the F13640 group, are displayed in the following Table:

	Placebo n*/N**	F13640 n/N
Dizziness	1/25	4/22
Headache	1/25	3/22
Pain	1/25	2/22
Nausea	-	2/22
Asthenia	-	2/22
Diarrhoea	3/25	-
Insomnia	2/25	-

*) **n = number of patients with adverse event by treatment group.**
) **N = number of patients by treatment group.

Conclusion

In conclusion, the descriptive analysis of the efficacy data did not allow to draw any meaningful conclusions on the efficacy of F13640 in this population. Regarding safety, TEAE observed were those commonly reported on F13640. The tolerability of F13640 (in patients treated at least 4 weeks), allowed an increase of doses up to 2 $mg.day^{-1}$.

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