Pierre Fabre Médicament
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1. TITLE PAGE

CLINICAL STUDY REPORT

A EUROPEAN PHASE III, MULTICENTRE, DOUBLE-BLIND, RANDOMISED, MONOTHERAPY, 12-MONTH STUDY OF MILNACIPRAN FOR THE TREATMENT OF THE FIBROMYALGIA SYNDROME

Investigational Product: Milnacipran 100, 150, and 200 mg/day

Protocol Number: F02207 GE 3 04

Phase of Development: III

Date of First Enrolment: 19 September 2006

Date of Last Completed: 02 October 2008

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Date of Report: May 5, 2009

Study performed in compliance with Good Clinical Practice.

2. SYNOPSIS

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

Title of study:	**A EUROPEAN PHASE III, MULTICENTRE, DOUBLE-BLIND, RANDOMISED, MONOTHERAPY, 12-MONTH STUDY OF MILNACIPRAN FOR THE TREATMENT OF THE FIBROMYALGIA SYNDROME**	
Investigators: **International Coordinating Investigator**	156 Investigators in 11 countries: Czech Republic (CR), Finland (FI), France (FR), Germany (G), Italy (I), Norway (N), Poland (POL), Portugal (POR), Romania (R), Spain (SP), and Sweden (SW). Prof. Jaime C. Branco - Serviço de Reumatologica, Centro Hospitalar de Lisboa Ocidental, EPE-Hospital Egas Moniz, 1349 – Lisboa, Portugal	
Study centres:	70 centres initiated and recruited	
Publication (reference):	N/A	
Study period: **Date of first enrolment** **Date of last completed**	2 years: 19 September 2006 02 October 2008	**Phase of development:** III
Objectives:	**Primary:** To assess the long-term safety of milnacipran used for the treatment of fibromyalgia (FM) at the target doses of 100, 150 and 200 mg/day. **Secondary:** To investigate the long-term efficacy (including the durability of efficacy) of milnacipran in treating FM over 12 months of exposure at the target doses of 100, 150 and 200 mg/day.	
Methods:	**Study Design** European, multicentre, randomised, double-blind, 3-parallel-arm, 1-year study of milnacipran 100, 150, and 200 mg/day, carried out as an extension study of the 17-week F02207 GE 3 02 lead-in phase III study of milnacipran 200 mg/day. **Treatment Allocation** Patients who had received milnacipran 200 mg/day in the lead-in study were allocated the same 200 mg/day dose in double-blind conditions. Patients who had received placebo in the lead-in study were randomised to receive either milnacipran 100, 150 or 200 mg/day in a 1:1:1 ratio in double-blind conditions. Each dose was given in two daily administrations; morning and evening. **Treatment Schedule** Patients were scheduled to receive 12 months of milnacipran therapy, consisting of: • an initial 4-week dose escalation phase from 25 mg/day up to the target dose; • a 48-week target dose phase (100, 150 or 200 mg/day); • a 9-day down titration phase. During the target dose phase, patients could have their dose reduced once by 50 mg/day in case of tolerability issue. **Visits** Twelve visits were scheduled: the screening visit (Day –7, which was the last visit of the F02207 GE 3 02 lead-in study), the inclusion visit (Day 1), Week 4 (end of dose escalation), Week 8, Week 12, Week 20, Week 28, Week 36, Week 44, Week 52 (end of target dose phase) or premature withdrawal (PW) visit, Week 52 (or PW) + 9 days (end of down titration), and Week 52 (or PW) + 3 weeks and 2 days (end of follow-up). Unscheduled visits could occur during the escalation phase or 48-week target dose phase in the case of patient tolerability concerns or for dose adjustments.	
Number of Patients:	Of the 678 patients (370/placebo, 308/milnacipran) who completed the lead-in study, **468** patients entered the extension study and were randomised and treated (91 with milnacipran 100 mg/day, 92 with milnacipran 150 mg/day, and 285 with milnacipran 200 mg/day [87 and 198 previously treated with placebo and milnacipran in the lead-in study, respectively]) The by-country distribution of the patients randomised was: 41 (CR), 94 (FR), 41 (SP), 32 (FI), 27 (G), 56 (I), 34 (N), 17 (POL), 4 (POR), 38 (R), and 84 (SW).	

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Diagnosis and Main Criteria for Inclusion:

- Male or female patients aged between 18 and 71 years;
- Diagnosis of FM per the American College of Rheumatology (ACR) criteria of 1990 at entry in the lead-in study;
- Having completed the 3-month lead-in study;
- Able to attend the screening visit on the day of the last visit of the lead-in study;
- (For women) with no childbearing potential or using a medically acceptable form of contraception;
- Beck Depression Inventory (BDI) ≤ 25 and BDI-item 9 (self-punitive wishes) ≤1 at screening and inclusion;
- Willing to carry on with withdrawal from central nervous system (CNS) active therapies commonly used for FM (including antidepressants, anticonvulsants, and opioids), and from trigger point and tender point injections, acupuncture, and anaesthetics.

Test Product: Milnacipran capsules of 25 mg and 50 mg

Dose: From 25 to 200 mg/day (b.i.d. administration from 50 mg/day), according to the following schedule:

	Study phase	**Duration**	**Total daily dose**		
			Treatment group		
			200 mg	**150 mg**	**100 mg**
Step 1	**Dose escalation**	2 days	25 mg		
Step 2		5 days	50 mg		
Step 3		7 days	100 mg		
Step 4		7 days	150 mg	150 mg	100 mg
Step 5		7 days	200 mg	150 mg	100 mg
Step 6	**Target dose**	48 weeks			
Step 7	**Down titration**	3 days	150 mg	100 mg	50 mg
Step 8		3 days	100 mg	50 mg	Placebo
Step 9		3 days	50 mg	Placebo	Placebo

Mode of Administration: Oral route, morning and evening during meals

Batch Numbers: 25 mg: SB0396,
50 mg: SB0394

Other Product, N/A

Duration of Treatment: Approximately 12 months (53 weeks and 2 days)

Other Product: Placebo capsules matching milnacipran capsules of 25 mg and 50 mg (used to maintain the blind between milnacipran treatments).

Dose: N/A

Mode of Administration: Oral route, morning and evening during meals

Batch Numbers: 25 mg: SB0398
50 mg: SB0397

Criteria for Evaluation:

Efficacy:

All efficacy parameters were recorded on the case report form.

All efficacy criteria were secondary, as the primary objective of this study was the assessment of safety. The main efficacy criterion was a 2-measure composite criterion defined by the responder status after 12 months of target dose based on weekly recall pain VAS and PGIC.

A patient was classified as a responder on the 2-measure composite criterion if she/he reached Week 4 (end of dose escalation), achieved a pain reduction ≥ 30% between the inclusion visit of the lead-in study (Baseline 302) and the end of the target dose phase (Week 52/PW), had a PGIC score of 1 or 2 (very much improved or much improved) at Week 52/PW, and had not taken non-allowed medication during one week prior to Week 52/PW.

Other efficacy criteria assessed were the Fibromyalgia Impact Questionnaire (FIQ), weekly-recall fatigue VAS, weekly-recall sleep VAS, Brief Pain Inventory-Short Form (BPI-SF), Beck Depression Inventory (BDI), State Trait Anxiety Inventory (STAI), Short-Form-36 (SF-36), Multiple Ability Self-Report Questionnaire (MASQ) and the Multidimensional Fatigue Inventory (MFI).

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Criteria for Evaluation: **Safety:**	All safety parameters were recorded on the case report form. ***Adverse events (AEs)****:* continuous assessment from screening. ***Physical exam***, complete physical examination, including weight at the screening visit and all subsequent scheduled and unscheduled visits ***Vital signs*** Standing and supine blood pressure (BP) and heart rate (HR) at the screening visit and all subsequent scheduled and unscheduled visits. ***Electrocardiogram (ECG)***: Standard 12-lead ECGs were carried out after 10 minutes in supine position at screening, the end of dose escalation (Week 4), Week 28 and Week 52/PW visits. ***Lab tests***: Blood and urine samples for haematology and clinical chemistry assessments were collected at screening, Week 4, Week 28 and Week 52/PW. A urine β-human chorionic gonadotrophin (β-HCG) was carried out in females of childbearing potential at the inclusion visit, the end of the down-titration phase (or the end of the target dose phase if the patient did not enter the down titration phase), and Week 56. ***Concomitant treatments***: continuous assessment from screening
Statistical Methods: **Efficacy:**	The assessment of efficacy was a secondary objective of this study. All efficacy analyses were carried out on the full analysis set (FAS). The following analyses were carried out on the composite criterion: Composite response at endpoint (Week 52/PW), composite response over time for all visits from Inclusion to Week 52, time to onset of response, durability of response (assessed by calculating the percentage of visits from Week 8 to Week 52 at which each patient was a responder), and time to loss of therapeutic response (LTR, defined as the first visit of two consecutive visits with non-response in the target dose phase) in the subgroup of patients who were responders on the composite criterion at ≥1 of the first 3 on-treatment visits (Week 4, 8 or 12) were provided by treatment group. The components of the composite criterion (i.e. pain and PGIC) were also described separately by treatment group at the end of target dose phase (Week 52/PW) and at each visit during and after the target dose period. For pain response and PGIC response, the durability, time to onset of response and time to LTR were provided by treatment group. For each secondary criterion, the following analyses were carried out: tabulated description of average values, changes from Baseline 302 and from Baseline 304 by treatment group at the end of target dose phase (Week 52/PW) using LOCF approach, changes over time from Baseline 302 and from Baseline 304 to Week 52/PW by treatment group and assessment time and graphical description of average values over time from Baseline 302 to Week 52/PW by treatment group and assessment time for the most important criteria. The relationship between dose and weekly-recall pain VAS was explored based on linearity and deviation from linearity tests on the subgroup of patients who received placebo in the lead-in study, at Week 52/PW using ANCOVA and Over Time using MMRM.
Safety:	The assessment of safety was the primary objective of this study. ***AEs,*** summarized as follows: - Number of patients, with at least one: AE, treatment emergent AE (TE AE), serious AE (SAE), AE leading to a definite study drug discontinuation, TE AE with a potential relationship to the study drug, AE leading to study drug change in dose (temporary or definitively), AE leading to definite study drug discontinuation after change in dose; - TE AEs tabulated by System Organ Class (SOC), High Level Group Term (HLGT), Preferred Term (PT) of MedDRA and treatment sequence, showing the maximum intensity, the most severe relationship to the study drug, minimal onset time and maximum duration; - Tabulated individual data for SAEs, AEs leading to definite study drug discontinuation and AEs leading to change in dose. ***Lab tests*****:** Descriptive statistics for values and changes from Baseline 302, scatter plots showing global trends and outliers, shift tables showing frequency of patients with on-treatment changes from Baseline 302 within and above normal laboratory ranges and tabulated individual data for clinically noteworthy abnormal laboratory values (CNALV); number of patients with elevated hepatic enzyme or total bilirubin levels. ***Vital Signs*****:** Descriptive statistics for values and changes from Baseline 302. Tabulated individual data for predefined potentially clinically significant changes (PCs) and PCs leading to predefined potentially clinically significant values (CSCs); change of hypertension status and maximal change (toward increase) of vital sign measurements. ***Physical exam*****:** Number of changes of general physical status (normal / abnormal); ***Weight:*** Descriptive statistics for values and changes from Baseline 302 at each evaluation time; ***ECG*****:** Descriptive statistics for values and changes from Baseline 302 at each evaluation time, for HR, QTc (Bazett and Fridericia formulae: QT_{CB}, and QT_{CF} respectively); ***Concomitant Treatments:*** Number of patients by WHO-DRUG ATC classes.

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Summary - Conclusions:

Patient Disposition:

490 screened, 468 (95.5%) randomised, 468 treated. All of the 468 patients who were randomized were included in the FAS

Patient disposition from randomisation is given in the following table (several reasons may have led to premature withdrawal):

Randomised	**Pbo - Mln100 n=91**		**Pbo - Mln150 n=92**		**Pbo - Mln200 n=87**		**Mln200-Mln200 n=198**		**Total n=468**	
Number of withdrawn patients	**40**	***(44.0%)***	**41**	***(44.6%)***	**35**	***(40.2%)***	**69**	***(34.8%)***	**185**	***(39.5%)***
Adverse Event	30	*(33.0 %)*	35	*(38.0 %)*	26	*(29.9 %)*	43	*(21.7 %)*	134	*(28.6 %)*
Therapeutic Failure	13	*(14.3 %)*	6	*(6.5 %)*	10	*(11.5 %)*	24	*(12.1 %)*	53	*(11.3 %)*
Patient's decision	19	*(20.9 %)*	21	*(22.8 %)*	18	*(20.7 %)*	40	*(20.2 %)*	98	*(20.9 %)*
Investigator's decision	5	*(5.5 %)*	10	*(10.9 %)*	5	*(5.7 %)*	18	*(9.1 %)*	38	*(8.1 %)*
Other	1	*(1.1 %)*	2	*(2.2 %)*	2	*(2.3 %)*	6	*(3.0 %)*	11	*(2.4 %)*
Completers	**51**	***(56.0%)***	**51**	***(55.4%)***	***52***	***(59.8%)***	***129***	***(65.2%)***	**283**	***(60.5%)***

Demographics and Other Baseline Characteristics

The demographics of the four treatment groups were comparable for all parameters reported. The majority of patients were females (93.6%) and were Caucasian (99.1%). The mean age was 49.7 years, mean height was 164.1 cm, mean weight was 72.2 kg and mean BMI was 26.8 kg/m^2. Patient medical and surgical history was similar across the four treatment groups.

The groups were similar in terms of the mean length of time since the onset of widespread pain (8.2 years overall) and the mean number of painful tender point sites (16.0 overall).

Efficacy results

Composite, Pain, and PGIC Responses

The results of the composite responder, pain and PGIC analyses are summarised in the table below:

	Placebo/ Milnacipran 100/mg/day	**Placebo/ Milnacipran 150/mg/day**	**Placebo/ Milnacipran 200/mg/day**	**Milnacipran 200 mg/day throughout**
Composite Response n	91	92	87	198
n (%) responders on Day 1	10 (11.0%)	15 (16.3%)	10 (11.5%)	30 (15.2%)
n (%) responders at Week 52 (LOCF)	25 (27.5%)	29 (31.5%)	28 (32.2%)	71 (35.9%)
n (%) of additional responders from Day 1 to Week 52 (LOCF)	15 (16.5%)	14 (15.2%)	18 (20.7%)	41 (20.7%)
Durability of Composite Response				
n Responders at Week 4, 8 or 12	34	41	31	93
• n (%) who remained responders at ≥ 80% of subsequent visits	14 (41.2%)	19 (46.3%)	17 (54.8%)	45 (49.5%)
• n (%) who remained responders at < 50% of subsequent visits	8 (23.5%)	15 (36.6%)	5 (16.1%)	24 (26.4%)
• n (%) who had no LTR	12 (35.3%)	16 (39.0%)	14 (45.2%)	41 (44.1%)
Pain n	89 (88 at Week 52)	91	87	196
% pain responders on Day 1	24 (27.0%)	31 (34.1%)	26 (29.9%)	61 (31.1%)
% pain responders at Week 52 (LOCF)	41 (46.6%)	54 (59.3%)	48 (55.2%)	114 (58.2%)
% of additional pain responders from Day 1 to Week 52 (LOCF)	17 (19.3%)	23 (25.3%)	22 (25.3%)	53 (27.0%)
Durability of Pain Response				
n pain responders at Week 4, 8 or 12	53	65	61	139
• n (%) who remained responders at ≥ 80% of subsequent visits	24 (47.1%)	36 (58.1%)	36 (61.0%)	78 (57.4%)
• n (%) who remained responders at < 50% of subsequent visits	11 (21.6%)	12 (19.4%)	10 (16.9%)	25 (18.4%)
• n (%) who had no LTR	18 (34.0%)	28 (43.1%)	31 (50.8%)	70 (50.4%)
Change in mean weekly-recall pain VAS score at Week 52 (LOCF):				
From Baseline 302 (mean [SD])	-20.9 (25.5)	-27.9 (27.0)	-26.6 (26.8)	-26.5 (29.0)
From Baseline 304 (mean [SD])	-11.6 (22.6)	-13.5 (22.5)	-15.3(22.5)	-14.7 (24.2)
PGIC n	91 (90 at Week 52)	92	87	198
% PGIC responders on Day 1	18 (19.8%)	26 (28.3%)	15 (17.2%)	73 (36.9%)
% PGIC responders at Week 52 (LOCF)	33 (36.7%)	35 (38.0%)	32 (36.8%)	87 (43.9%)
% of additional PGIC responders from Day 1 to Week 52 (LOCF)	15 (16.7%)	9 (9.8%)	17 (19.5%)	14 (7.1%)
Durability of PGIC Response				
n PGIC responders at Week 4, 8 or 12	40	47	36	108
• n (%) who remained responders at ≥ 80% of subsequent visits	28 (70.0%)	25 (54.3%)	22 (61.1%)	64 (60.4%)
• n (%) who remained responders at < 50% of subsequent visits	9 (22.5%)	8 (17.4%)	7 (19.4%)	22 (20.8%)
• n (%) who had no LTR	23 (57.5%)	23 (48.9%)	19 (52.8%)	56 (51.9%)

- On Day 1 the proportion of composite, pain and PGIC responders were not relevantly different between groups.
- The proportion of composite, pain and PGIC responders increased between Day 1 and Week 52 in all groups.
- The greatest increases in the proportion of composite responders from Day 1 to Week 52 occurred with milnacipran 200 mg/day, regardless of the treatment received in the lead-in study.
- Time to onset of composite response was shortest in the milnacipran 200 mg/day throughout group than in the groups where patients had received placebo in the lead-in study, and time to onset of pain response was shortest in the groups where patient had received milnacipran 200 mg/day (regardless of the treatment received in the lead-in study). Time to onset of PGIC response was similar across the treatment groups.

Name of Company: Pierre Fabre Médicament	**Individual Study Table Referring to Module 5 of the Dossier Vol.: .....Page: .....**	**(For National Authority Use Only)**
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Summary – Conclusions (*continued*)**:**

Efficacy results (*continued*)

Composite, Pain, and PGIC Responses (*continued*)

- The durability of composite response was highest with milnacipran 200 mg/day (regardless of treatment in the lead-in study).
- The proportion of patients who were responders at Weeks 4, 8 or 12 and maintained that response for > 80% of subsequent visits was > 41% for composite response, > 47% for pain response and >54.3% for PGIC response.
- The highest proportion of patients who responded during the first 3 months and had no loss of composite response or PGIC response was seen in the milnacipran 200 mg/day throughout group and the highest proportion who had no loss of pain response was in the groups of patients who received milnacipran 200 mg/day regardless of the treatment they received in the lead-in study.
- In all groups, the greatest increase in the proportion of composite, pain and PGIC responders occurred in the first 8 weeks of the study. The greatest increase in all groups in the proportion of PGIC improvers occurred within the first 4 weeks.
- All groups showed a reduction (improvement) in mean pain VAS score between Baseline and Week 52 (LOCF).

Secondary Variables

The key results of the secondary efficacy analyses are presented in the table below:

	Placebo/ Milnacipran 100/mg/day	**Placebo/ Milnacipran 150/mg/day**	**Placebo/ Milnacipran 200/mg/day**	**Milnacipran 200 mg/day throughout**
Pain				
24-hour-recall pain change at Week 52 (LOCF):				
From Baseline 302 (mean [SD])	-23.3 (26.6)	-25.7 (26.9)	-27.5 (26.2)	-26.9 (27.6)
From Baseline 304 (mean [SD])	-14.3 (22.7)	-14.2 (23.6)	-16.6 (22.1)	-14.1 (23.5)
FIQ pain change at Week 52 (LOCF):				
From Baseline 302 (mean [SD])	-18.2 (27.5)	-23.5 (24.9)	-23.5 (25.2)	-24.8 (28.3)
From Baseline 304 (mean [SD])	-12.1 (22.7)	-13.0 (22.2)	-15.4 (22.0)	-15.9 (24.6)
SF-36-BP change at Week 52 (LOCF):				
From Baseline 302 (mean [SD])	13.18 (22.13)	14.22 (23.11)	14.69 (21.70)	14.79 (21.85)
From Baseline 304 (mean [SD])	7.33 (21.45)	8.78 (19.24)	9.29 (19.29)	8.52 (21.81)
BPI pain intensity change at Week 52 (LOCF):				
From Baseline 302 (mean [SD])	-1.47 (2.24)	-1.82 (2.02)	-1.79 (1.98)	-1.95 (2.34)
From Baseline 304 (mean [SD])	-0.98 (1.95)	-1.18 (1.98)	-1.17 (1.82)	-1.21 (1.91)
BPI pain interference change at Week 52 (LOCF):				
From Baseline 302 (mean [SD])	-1.31 (2.19)	-1.35 (2.41)	-1.92 (2.07)	-1.68 (2.42)
From Baseline 304 (mean [SD])	-0.57 (1.87)	-0.41 (1.86)	-0.93 (1.78)	-0.91 (1.96)
QOL functional status				
FIQ-total change at Week 52 (LOCF):				
From Baseline 302 (mean [SD])	-11.72 (21.66)	-17.79 (20.77)	-16.21 (19.19)	-17.06 (22.02)
From Baseline 304 (mean [SD])	-6.02 (16.53)	-9.19 (16.38)	-7.90 (13.76)	-9.30 (18.05)
SF-36-PCS change at Week 52 (LOCF) to:				
From Baseline 302 (mean [SD])	4.38 (7.19)	3.94 (8.54)	4.23 (7.22)	4.96 (7.74)
From Baseline 304 (mean [SD])	2.47 (6.60)	2.28 (6.17)	2.28 (6.01)	2.72 (6.57)
Fatigue				
Total MFI change at Week 52 (LOCF):				
From Baseline 302 (mean [SD])	-3.93 (16.25)	-6.69 (14.39)	-6.44 (16.81)	-6.71 (16.27)
From Baseline 304 (mean [SD])	-2.77 (13.93)	-2.32 (13.25)	-2.25 (13.57)	-3.25 (12.57)
Weekly-recall fatigue change at Week 52 (LOCF):				
From Baseline 302 (mean [SD])	-15.8 (27.1)	-22.0 (30.1)	-20.9 (23.4)	-20.4 (30.4)
From Baseline 304 (mean [SD])	-8.3 (22.8)	-14.2 (24.9)	-9.6 (18.9)	-10.3 (25.3)
FIQ-overall fatigue change at Week 52 (LOCF):				
From Baseline 302 (mean [SD])	-14.3 (29.4)	-24.4 (28.2)	-21.1 (24.4)	-22.5 (30.2)
From Baseline 304 (mean [SD])	-6.7 (23.8)	-14.4 (23.9)	-10.1 (19.1)	-12.1 (25.4)
Sleep				
Weekly-recall sleep change at Week 52 (LOCF):				
From Baseline 302 (mean [SD])	-11.9 (26.5)	-21.1 (28.6)	-20.2 (24.6)	-19.9 (30.7)
From Baseline 304 (mean [SD])	-6.6 (24.0)	-13.6 (27.1)	-9.2 (17.8)	-10.9 (26.7)

- Pain: An improvement in pain from Baseline 302 and Baseline 304 to Week 52 was shown with all variables assessed (24-recall and current pain VAS scores, FIQ pain, SF-36-BP, BPI pain intensity and BPI pain interference). Where there was a difference between treatment groups, the greatest improvement was always seen with milnacipran 200 mg/day (FIQ pain, BPI pain intensity and BPI pain interference).
- QOL functional status: Overall there was a general trend of improvement in QOL functional status (as measured by FIQ-total score and SF-36-PCS) from Baseline 302 and Baseline 304 to Week 52. These improvements were generally similar in all groups (except for the placebo/milnacipran 100 mg/day group where the improvement in FIQ-total score from Baseline 302 to Week 52 was smaller than in the other groups).
- Fatigue: An improvement in fatigue from Baseline 302 and Baseline 304 to Week 52 was shown with all variables assessed (MFI, weekly-recall fatigue VAS and FIQ overall fatigue). From Baseline 302 to Week 52 all three variables showed a smaller improvement in fatigue in the placebo/milnacipran 100 mg/day group than in the other groups. The change from Baseline 304 to Week 52 in MFI was similar in all groups whilst the change in weekly-recall fatigue and FIQ overall fatigue during showed some variation between groups, but did not indicate any clear dose response.

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Name of active substance *(or ingredient)***:** Milnacipran hydrochloride	**Vol.: .....Page: .....**	

Summary – Conclusions (*continued*)**:**

Efficacy results (*continued*)

Secondary Variables(*continued*)

- Sleep: All treatment groups showed an improvement (decrease) in weekly-recall sleep VAS score from Baseline 302 and Baseline 304 to Week 52, and these changes were smallest in the placebo/milnacipran 100 mg/day group.

During this extension study, there were no clinically relevant changes in depression (BDI and FIQ depression score), anxiety (FIQ-anxiety and STAI-S scores) and QOL functional status as measured by MASQ-total and SF-36-MCS scores.

Safety results

None of the safety assessments showed a trend for a decrease in safety and tolerability with extended treatment with milnacipran over a one year period. There was no increase in the frequency of any AEs, laboratory CNALVs, vital sign CSCs or abnormal ECGs over time.

Summary of Adverse Events

Almost all patients had at least one TE AE (91.7%) and the majority also had at least one treatment related TE AE (78.0%). There was no dose response in the overall number of TE AEs, the number of related TE AEs or the number of AEs leading to discontinuation.

Most Common Adverse Events

The most common treatment related AEs (reported in ≥ 5% of patients in any group) were, in decreasing order for all patients:

Preferred Term	Pbo - Mln100 n=91		Pbo - Mln150 n=92		Pbo - Mln200 n=87		Mln200-Mln200 n=198		Total n=468	
Hyperhidrosis	23	(25.3 %)	24	(26.1 %)	21	(24.1 %)	37	(18.7 %)	105	(22.4 %)
Nausea	18	(19.8 %)	17	(18.5 %)	24	(27.6 %)	34	(17.2 %)	93	(19.9 %)
Headache	17	(18.7 %)	17	(18.5 %)	19	(21.8 %)	29	(14.6 %)	82	(17.5 %)
Tachycardia*	17	(18.7 %)	15	(16.3 %)	15	(17.2 %)	23	(11.6 %)	70	(15.0 %)
Hypertension**	12	(13.2 %)	12	(13.0 %)	11	(12.6 %)	26	(13.1 %)	61	(13.0 %)
Constipation	14	(15.4 %)	6	(6.5 %)	10	(11.5 %)	16	(8.1 %)	46	(9.8 %)
Dizziness	5	(5.5 %)	16	(17.4 %)	6	(6.9 %)	9	(4.5 %)	36	(7.7 %)
Palpitations	4	(4.4 %)	8	(8.7 %)	5	(5.7 %)	13	(6.6 %)	30	(6.4 %)
Hot flush	7	(7.7 %)	5	(5.4 %)	7	(8.0 %)	7	(3.5 %)	26	(5.6 %)
Insomnia	5	(5.5 %)	1	(1.1 %)	3	(3.4 %)	10	(5.1 %)	19	(4.1 %)
Abdominal pain upper	2	(2.2 %)	6	(6.5 %)	3	(3.4 %)	5	(2.5 %)	16	(3.4 %)
Dry mouth	1	(1.1 %)	4	(4.3 %)	5	(5.7 %)	6	(3.0 %)	16	(3.4 %)
Vomiting	2	(2.2 %)	3	(3.3 %)	5	(5.7 %)	6	(3.0 %)	16	(3.4 %)

(*) Tachycardia includes the following Preferred Terms: Tachycardia, Sinus tachycardia, Heart rate increased

(**) Hypertension include the following Preferred Terms: Hypertension, Hypertensive crisis, Malignant hypertension, Hypertensive cardiomyopathy, Blood pressure increased, Blood pressure diastolic increased

(***) Hypotension includes the following Preferred Terms: Hypotension, Orthostatic hypotension, Blood pressure decreased

Less frequent clinically relevant TE AEs were: ALAT increase in 1 patient (0.2%), hepatic enzyme increase in 1 patient (0.2%), hepatomegaly in 3 patients (0.6%), cytolytic hepatitis in 1 patient (0.2%) and, in male patients, dysuria (6/30, 20.0%), penile pain (1/30, 3.3%) and scrotal pain (1/30, 3.3%).

The most common AEs which led to dose reduction (in ≥ 1% of patients) or discontinuation (in ≥ 1% of patients) were, in decreasing order overall: hyperhidrosis, nausea, tachycardia, headache, hypertension, dizziness, palpitations, blood pressure increased, heart rate increased, fibromyalgia (discontinuation only), constipation and hot flush. The lowest proportion of patients who had a dose reduction or discontinued the study due to AEs was in the milnacipran 200 mg/day throughout group. The proportion of patients who had AEs which led to dose reduction ranged from 20.7% to 30.8% across the treatment groups, and the proportion who had AEs which led to discontinuation ranged from 21.7% to 38.0%.

Of the 115 (/468, 24.6%) patients who had a dose reduction due to an AE, 31 (/115, 27.0%) subsequently discontinued due to that AE.

The most common time of onset for most TE AEs of interest (including the most common TE AEs) was during the dose escalation phase. There was no evidence of an increase in incidence of any of clinically relevant TE AEs with increased exposure.

The frequency and types of post-treatment emergent AEs reported do not suggest any adverse symptoms to withdrawal from milnacipran.

Serious Adverse Events

There were no deaths during the study. Overall 39 patients experienced a total of 42 SAEs: 16/198 (8.1%) patients in the milnacipran 200 mg/day throughout group, 4/87 (4.6%) patients in the placebo/milnacipran 200 mg/day group, 13/92 (14.1%) patients in the placebo/milnacipran 150 mg/day group and 6/91 (6.6%) patients in the placebo/milnacipran 100 mg/day group.

SAEs which, in the Investigator's opinion, had a non-excluded or unassessable relationship to the study drug were reported in:

- 3 patients in the milnacipran 200 mg/day throughout group: 1 event each of severe angioneurotic oedema, severe aortic dissection and severe macular hole;
- 1 patient in the placebo/milnacipran 200 mg/day group: 1 event of severe vertigo;
- 3 patients in the placebo/milnacipran 150 mg/day group, 1 event each of: severe serotoninergic manifestations, increase in blood creatine phosphokinase and severe gastritis;
- 1 patient in the placebo/milnacipran 100 mg/day group: 1 event of severe cardiac failure.

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

Summary – Conclusions (*continued*)**:**

Clinical Laboratory Evaluation

On-treatment haematology CNALVs (decreases) were reported in the following:

- haemoglobin CNALVs in 1 patient at Week 28 in the placebo/milnacipran 100 mg/day group,
- neutrophil CNALVs in 6 patients: 2 patients in the placebo/milnacipran 100 mg/day group (1 at Week 43 and 1 at Week 52), 3 patients in the placebo/milnacipran 150 mg/day groups (2 at Week 4 and 1 at Week 52) and 1 patient in the placebo/milnacipran 200 mg/day group (at Week 52).
- platelet CNALVs in 3 patients.

None of the haematology CNALVs were reported as AEs.

No CNALVs occurred in ALP or γGT.

Two patients had on-treatment CNALVs of both ASAT and ALAT (> 2 N): 1 patient in the placebo/milnacipran 100 mg/day group had CNALVs of ASAT (186 U/L) and ALAT (273 U/L) at Week 28 which were reported as TE AEs, and 1 patient in the milnacipran 200 mg/day throughout group had a CNALV of ALAT (105 U/L) at Week 52, which had risen further one week later (to 250 U/L), at which time she also had a CNALV of ASAT (112 U/L). In addition, 1 patient had an on-treatment ASAT (149 U/L) CNALV (in the placebo/milnacipran 150 mg/day group at Week 4) and 4 patients had on-treatment ALAT CNALVs (1 in the placebo/milnacipran 100 mg/day group at Week 4, and 3 in the milnacipran 200 mg/day throughout group, 1 at Week 4 and 2 at Week 52). All of these CNALVs occurred from normal levels at Baseline 302 and Screening.

On-treatment Bilirubin CNALVs (> 1.5 N) occurred in 2 patients in total, 1 in the placebo/milnacipran 200 mg/day group (46 µmol/L) and 1 in the milnacipran 200 mg/day throughout group (70 µmol/L) from normal levels at Baseline 302 and Screening. None of these CNALVs were reported as TE AEs.

Vital Signs

The time profiles of mean vital sign changes were generally similar across the treatment groups with an increase from baseline in either parameter generally reaching its maximum around Weeks 8-12, and a return towards baseline values at the end of the post-treatment follow-up period.

Maximum mean increases overall were: +2.7 mmHg, +3.2 mmHg and +10.6 bpm for SBP, DBP and HR, respectively.

There was no dose response in the proportion of patients who had PCs of an increase or decrease in SBP, DBP and HR. The vital sign CSC which occurred the most frequently was CSC increase in DBP (in 3.2% of patients). Of the 24 patients who had CSC increases in SBP or DBP, ~60% had relevant concomitant diseases or medical history from prior to the start of this extension study.

The maximum increases in SBP and DBP were similar across all treatment groups. For SBP, 65.8% of patients had a maximum increase ≥ 10 mmHg and 3.8% of patients had a maximum increase of ≥ 40 mmHg. For DBP, 54.3% of patients had a maximum increase ≥ 10 mmHg and 3.4% of patients had a maximum increase of ≥ 30 mmHg. For HR, 80.3% of patients in the milnacipran 200 mg/day throughout group had a maximum increase of ≥ 10 bpm compared with 67.8%, 66.3% and 72.5% in the placebo/milnacipran 200, 150 and 100 mg/day groups respectively. The proportion of patients in each group who had maximum increases in HR ≥ 20 bpm and ≥ 30 bpm were similar across all groups (44.9% and 20.1% overall respectively).

ECG

Three patients had on-treatment changes in QT_{CB} ≥ 60 ms; 2 females (increases of 62 and 67 ms) in the placebo/milnacipran 200 mg/day group (both at Week 52) and 1 female (increase of 63 ms)in the placebo/milnacipran 100 mg/day group (at Week 28). The two patients in the placebo/milnacipran 200 mg/day group each also had concomitant cardiac TE AEs (tachycardia hypertensive in one patient and cardiomyopathy in the other). One patient, a female in the milnacipran 200 mg/day group, had an on-treatment change in QT_{CF} ≥ 60 ms (increase of 78 ms) which occurred at Week 52.

The proportion of ECG abnormalities reported by the cardiologist was not relevantly different between treatment groups (33.8% of patients overall). The most common ECG abnormalities reported were sinus tachycardia > 100 bpm (in 8.3% of patients) and non-specific T wave abnormality (7.3%). ECG abnormalities were only reported as TE AEs in 2 patients (one TE AE of bundle branch block and one of left anterior fascicular block).

Conclusion

This long term extension study shows the beneficial effect of milnacipran in FM and the maintenance of this effect over a-1-year period. This efficacy was observed on both the primary composite criterion and on each of its components. The safety profile seen in this study was satisfactory and no unexpected adverse reactions and/or safety findings were observed with long term administration of milnacipran for the treatment of FM.

Date of report: May 5, 2009