Pierre Fabre Médicament
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1. TITLE PAGE

CLINICAL STUDY REPORT

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

Investigational Product:	Milnacipran capsules 25 and 50 mg - target daily dose: 200 mg
Protocol Number:	F02207 GE 3 02
Phase of Development:	III
Date of First Enrolment:	21 Feb 2006
Date of Last Completed:	04 Sep 2007
Coordinator:	Prof. Jaime C. Branco *Serviço de Reumatologica,* *Centro Hospitalar de Lisboa Ocidental,* *EPE-Hospital Egas Moniz,* 1349 – *Lisboa*, Portugal Phone: 351 933 009 500
Sponsor Representatives for Study Report:	Program Director: Yves MAINGUY, MD – *IRPF* Phone: +33 (0)5 62 24 27 40 Study Manager: Martine GALISSIE – *IRPF* Phone: +33 (0)5 62 24 27 47 Project Statistician: Nicole PEZOUS – *Pierre Fabre Biométrie* Phone: + 33 (0)5 62 27 78 Medical Writer: Agnès MONTAGNE, MD – *IRPF* Phone: + 33 (0)5 62 24 27 38
Date of Report:	5 May 2008

Study performed in compliance with Good Clinical Practice.

2. SYNOPSIS

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: milnacipran	**Referring to Module 5 of the Dossier**	
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Title of study:	**A EUROPEAN PHASE III, MULTICENTRE, DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED, MONOTHERAPY STUDY OF MILNACIPRAN FOR THE TREATMENT OF THE FIBROMYALGIA SYNDROME**	
Investigators:	- 216 investigators potentially involved: • Mainly specialists in: rheumatology and pain management, • In 13 European countries: Czech Republic CR (13), Denmark D (5), Finland FI (13), France FR (61), Germany G (19), Italy I (28), Norway N (8), Poland POL (10), Portugal POR (7), Romania R (21), Spain SP (18), Sweden SW (9), and United Kingdom UK (4). - International Coordinating Investigator: Prof. Jaime C. Branco - *Serviço de Reumatologica, Centro Hospitalar de Lisboa Ocidental, EPE-Hospital Egas Moniz, 1349 – Lisboa*, Portugal	
Study centres:	- 89 recruiting centres • Hospital units (46), public clinics (19), private clinics (24), • FR (23), I (12), SP (8), POR (7), R (6), CR (6), G (6), FI (5), SW (4), POL (4), N (3), UK (3), and D (2). - 83 randomising centres: FR (22), I (11), SP (8), POR (6), R (6), G (6), CR (5), FI (5), SW (4), POL (4), N (3), D (2), and UK (1).	
Publication (reference):	**Branco J et al,** *Milnacipran for the treatment of fibromyalgia syndrome: a european multicenter, randomized, double-blind, placebo-controlled trial* Abstract accepted on 10 Apr 2008 by the EULAR Scientific Program Committee for a poster presentation (ref THU0365)	
Study period: **Date of first enrolment** **Date of last completed**	19 months 21 Feb 2006 04 Sep 2007	**Phase of development:** III
Objectives:	**Primary:** To demonstrate the efficacy of milnacipran 200 mg/day as compared to placebo in the treatment of the fibromyalgia syndrome (FMS) in outpatients after a 12-week period of fixed dose exposure through a primary composite criterion incorporating two domains: pain and patient global impression of change and a key secondary criterion measuring FMS impact on function and patient's activities of daily living. **Secondary:** • To compare the efficacy of 200 mg/day of milnacipran to placebo on a number of secondary endpoints, • To establish the safety profile of 200 mg/day of milnacipran in patients with FMS.	
Methods:	European, multicentre, randomised, double-blind, placebo-controlled, 2-parallel-arm. ***3-to-6-Week Selection Period:*** • Screening Visit (V1), • 1-to-4-week Wash Out Period of the current FMS treatment or any other drug that could potentially interfere with efficacy measurements, and • 2-week Baseline Period [V2/D-14 (BL1) to V3/D1 (BL2/Randomisation)]; Randomisation into either the Placebo or Milnacipran group, at a 1:1 ratio.	

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Methods (cont'd):	***17-Week (+2 days) Treatment Period:*** • 4-week Dose Escalation Phase [V3/D1 to V5/W4 (V4 optional between D10 and D27)], • 12-week Fixed-Dose Phase at 200 mg/day [V5-V6/W8-V7/W12-V8/W16], • 9-day Down-Titration Phase [V8-V9/W17+2 days]. ***2-Week Post-treatment Follow-Up Period*** [V9-V10/W19+2 days], free of treatment. Patient's Electronic Diary [PED (Palm pilot E2 or TW)] used for the Patient's self-assessment of most key measures including those of both primary outcomes.
Number of Patients:	884 randomised outpatients: • 449 into Placebo group and 435 into Milnacipran group • 184 (FR), 111 (SP), 20 (D), 60 (FI), 42 (G), 101 (I), 53 (N), 31 (POL), 16 (POR), 59 (R), 151 (SW), 55 (CR), and 1 (UK).
Diagnosis and Main Criteria for Inclusion:	Female or male patient aged 18-70 years with a diagnosis of FMS according to the 1990 ACR criteria, willing to withdraw from CNS-active therapies commonly used for FMS, without any severe psychiatric illness or significant suicidal risk, as attested by the MINI questionnaire. Cut-off values: Mean Daily VAS Pain over the Baseline Period of 40-to-90, FIQ-PF ≥ 3 at Randomisation, Beck Depression Inventory ≤ 25 at V2/W-4 and V3/W0.
Test Product, **Dose,**	Milnacipran capsules of 25 mg and 50 mg From 25 to 200 mg/day, according to the following schedule: ***4-week Dose Escalation Phase:*** • Step 1: 25 mg/d 2 days 25 mg pm (1 caps) • Step 2: 50 mg/d 5 days 25 mg am (1 caps), 25 mg pm (1 caps) • Step 3: 100 mg/d 7 days 50 mg am (1 caps), 50 mg pm (1 caps) • Step 4: 150 mg/d 7 days 50 mg am (1 caps), 100 mg pm (2 caps) • Step 5: 200 mg/d 7 days 100 mg am (2 caps), 100 mg pm (2 caps) ***12-week Fixed Dose Phase:*** • Step 6: 200 mg/d 12 weeks 100 mg am (2 caps), 100 mg pm (2 caps) ***9-day Down-Titration Phase:*** • Step 7: 150 mg/d 3 days 50 mg am (1 caps), 100 mg pm (2 caps) • 100 mg/d 3 days 50 mg am (1 caps), 50 mg pm (1 caps) • 50 mg/d 3 days 25 mg am (1 caps), 25 mg pm (1 caps)
Mode of Administration, **Batch Numbers:**	Oral route, morning and evening during meals, 25 mg: SB0396, 50 mg: SB0394, SB0484
Other Product:	N/A
Duration of Treatment:	17 weeks and 2 days including a 12-week Fixed Dose Phase at 200 mg/day
Control Therapy, **Dose,** **Mode of Administration,** **Batch Numbers:**	Placebo capsules matching milnacipran capsules of 25 mg and 50 mg See "Test Product, Dose", See "Test Product, Mode of Administration" Matching 25 mg milnacipran capsules: SB0398 Matching 50 mg milnacipran capsules: SB0397, SB0485

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Criteria for Evaluation Efficacy:

Primary Criterion:

Proportion of responders to treatment on the composite primary criterion at V8/Week 16 or PW*, i.e.*,

- with a reduction from baseline ≥ 30% in the ***24h-Recall Pain VAS$_{[0-100]}$*** (mean of the daily scores over the last 2 weeks) self-rated every morning on the PED,
- with ***Patient Global Impression of Change (PGIC)***, self- reported on the PED at the on-site visit, of '1' or '2' ("very much improved" and "much improved") on a 1-7 verbal numeric scale,
- having reached V5/W4 (end of Dose Escalation Phase),
- with at least seven available daily pain VAS scores over the last 2 weeks,
- not having taken during the End-of-Fixed-Dose period any of the following non-allowed medications for FMS indication: strong analgesic, antidepressant, mood stabilizer, anticonvulsant, anaesthetic, dopamine agonist.

Key Secondary Criterion:

Fibromyalgia Impact Questionnaire (FIQ) Total Score $_{[0-100]}$,, self-assessed on the PED at on-site visits from V3/W0 (weekly recall),

Secondary Outcomes Self-Assessed daily or weekly on the PED:

- ***Other Pain VAS$_{[0-100]}$***:
  - ***Current Daily Morning Pain,***
  - ***Current Daily Evening Pain,***
  - ***Weekly Recall Pain;***
- ***Other Single VAS $_{[0-100]}$***:
  - ***Weekly Recall Fatigue,***
  - ***Weekly Recall Sleep;***
- ***10 FIQ-derived scores: FIQ-PF$_{[0-3]}$*** *(measuring physical impairment,* ***Modified FIQ-Total$_{[0-80]}$*** ***(****i.e., FIQ-Total minus Well-Being Impairment and Work Missed);Good Days$_{[7-0]}$, Work-Missed Days$_{[0-7]}$, and 7 VAS$_{[0-100]}$:Difficulty with Work, Pain, Fatigue, Morning Tiredness, Stiffness, Anxiety, and Depression),*

Secondary Outcomes Self-Assessed on the CRF at on-site visits:

- ***Pain "Paper" VAS$_{[0-100]}$***: ***24h-Recall Pain*** and ***Weekly Recall Pain***;
- ***SF-36-derived Mental and Physical Component Summaries (MCS$_{[100-0]}$ and PCS$_{[100-0]}$)*** and ***8 dimension scores$_{[100-0]}$:*** *Physical Functioning, Role Limitation due to Physical Health, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitation due to Emotional Problems, Mental Health*;
- Cognitive ***Multiple Ability Self-Report Questionnaire*** (***MASQ***) ***Total Score $_{[38-190]}$***, and ***5 derived domain Scores $_{[1-5]}$***: *Language Ability, Visio-Perceptual Ability, Verbal Memory, Visual Memory, Attention*;
- ***Beck Depression Inventory (BDI$_{[0-63]}$)***;
- ***MFI-Total score $_{[20-100]}$ and 5 derived dimension scores$_{[4-20]}$***: *General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity*;
- ***Brief Pain Inventory (BPI)-SF***: ***Pain Intensity score$_{[0-10]}$*** and ***Pain Interference score $_{[0-10]}$*** (averaged over 7 domains: *General Activity, Mood, Walking Ability, Normal Work, Relations with Others, Sleep, Enjoyment of Life);*
- ***State Trait Anxiety Inventory (STAI) scores***: ***(STAI)-T$_{[20-80]}$*** (at V1/Screening only) and ***STAI-S$_{[20-80]}$***;

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Criteria for Evaluation - Efficacy (cont'd):	- ***Medical Outcomes Study*** (***MOS*****-*****Sleep***: 2 ***Indexes I and II***$_{[0\text{-}100]}$ and ***7 subscores***$_{[0\text{-}100]}$ (*Sleep Disturbance, Snoring, Awakening Short of Breath or with Headache, Quantity of Sleep, Optimal Sleep, Sleep Adequacy, Somnolence*). - ***Concomitant Treatments*** *for* ***Pain, Anxiety,*** and ***Sleep.***
Criteria for Evaluation - Safety:	- ***Adverse Events (AEs)****:* continuous assessment from V1/Screening, - ***General Physical Exam*** and ***Vital Signs*** (*Systolic/Diastolic Blood Pressures* and *Heart Rate*) at on-site visits from Screening, - ***ECG*** at V2-Week 4 (baseline), V5-Week 4, and V8-Week 16 or PW, - ***Lab Tests*** (*Standard Haematology + Coagulation Tests*, *Standard Biochemistry + CPK* and *TSH*): at V1/Screening, (baseline), V5-Week 4, and V8-Week 16 or PW, - ***Concomitant Treatments***: continuous assessment from V1/Screening.
Statistical Methods - Efficacy:	**Primary Analysis of the Primary Criterion:** - In the Full Analysis Set (FAS), on a last-observation-carried-forward (LOCF) basis, - Step 1: Logistic regression model on the responder rate on the primary composite criterion with baseline pain score as covariate and treatment as fixed factor, - Step 2: FIQ total score change from baseline to V8-Week 16: analysis of variance with covariate (ANCOVA) with baseline value as covariate, and treatment and country as fixed factors, **Supportive Analyses of the Primary Analysis:** - Primary analysis performed on the Per Protocol (PP) data set, - Sensitivity Analyses: observed-case (OC), multiple-imputation (MI), and baseline observation-carried-forward (BOCF) approaches for missing data, other rules for pain data invalidated by the intake of a potentially result-confounding medication; **Additional Analyses relating to the Primary Criterion:** - Response on each component of the primary criterion; - Influence of baseline mood (BDI) and anxiety (STAI-S and STAI-T) on response on the primary criterion; **Analyses of Secondary Criteria** - ***Quantitative Criteria***: • Change from baseline to V8-LOCF: ANCOVA with Treatment and Country as factors and baseline value as covariate, • Evaluation over time : Mixed-effect Model for Repeated Measures (MMRM); - ***Qualitative Criteria***: Cochran-Mantel-Haenszel (CMH) test; - ***Concomitant Treatments for Pain, Anxiety or Sleep:*** descriptive comparison of frequencies by study periods up to V8-Week 16, and by empirical classes of duration of use; - ***2-Week Post-treatment Follow-Up Period***: descriptive statistics on changes from V3 and from V8 to V9 and to V10.

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Statistical Methods - Safety

- ***Length of Exposure:*** descriptive quantitative and qualitative statistics of global duration;
- ***AEs*:**
  - Number (N) (%) of patients: with at least one: AE, treatment-emergent AE (TEAE), serious AE (SAE), AE leading to a definitive study treatment discontinuation, TEAE by most severe intensity, TEAE by relationship to the study drug;
  - N (%) of patients with at least one TEAE by System Organ Class (SOC), by SOC High Level Group Term (HLGT) and Preferred Term (PT) of MedDRA;
  - Tabulated individual data for SAEs and for AEs leading to definitive study treatment discontinuation;
  - 2-Week post-treatment FU period: descriptive analysis of TEAEs;
- ***Lab Tests*:**
  - Descriptive statistics for values and changes over time,
  - N (%) of patients with: i/ potentially clinically significant change (PC), ii/ PC leading to out of range value (PCA),
  - Scatter plots as a function of baseline values for V8/PW values,
  - Tabulated individual data for clinically noteworthy abnormal lab values (CNALV);
- ***Vital Signs*:**
  - Descriptive statistics for values and changes over time,
  - N (%) of patients for: i) predefined potentially clinically significant changes (PC), ii) PC leading to predefined potentially clinically significant values (CSC);
- ***Weight***: Descriptive statistics for values and changes over time;
- ***Physical Exam*:** Number of changes of general physical status (normal / abnormal) over time;
- ***ECG*:**
  - N (%) of patients by treatment-emergent abnormalities on the Cardiologist's assessment,
  - QTc: N (%) of patients by CHMP categories of QTc-Bazett (QT_{CB}) and –Fridericia (QT_{CF}) values and changes from baseline;
- ***Concomitant Treatments:*** N (%) of patients by WHO-DRUG ATC classes.

Summary - Conclusions:

Patients (1/2)

Disposition

1406 patients were screened. Of them, 884 (62.9%) were randomised, and 881 patients received at least one dose of study treatment. There was no loss to follow-up. The patient disposition from randomisation to study completion was the following (several reasons may have led to a premature withdrawal):

	Placebo	**Milnacipran**
Randomised	**449**	**435**
Withdrawn (all)	***79 (17.6%)***	***127 (29.2%)***
- *Adverse event*	*44 (9.8%)*	*96 (22.1%)*
- *Therapeutic failure*	*33 (7.3%)*	*24 (5.5%)*
- *Patient's decision*	*38 (8.5%)*	*66 (15.2%)*
- *Investigator's decision*	*10 (2.2%)*	*20 (4.6%)*
- *Sponsor's decision*	*2 (0.4%)*	*1 (0.2%)*
- *Other*	*7 (1.5%)*	*18 (4.1%)*
Completers	**370 (82.4%)**	**308 (70.8%)**

Safety, FAS and PP data sets included 877 (446 placebo/431 milnacipran), 876 (446 placebo /430 milnacipran) and 715 (380 placebo /335 milnacipran) patients, respectively.

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Patients (2/2)

Demographics and Other Baseline Characteristics

Both groups were similar with respect to demographics and FMS history.

The mean age (sd) of the FAS sample was of 48.8 (9.8) years. The female ratio was of 94.3%, and the mean (sd) body mass index (BMI) of 26.7 (5.2) kg/m^2. The proportion of obese patients (BMI ≥ 30) was of 22.3%. The mean (sd) duration of the fibromyalgia symptomatology and of the FMS diagnosis were of 9.5 (8.6) and 4 (4.7) years, respectively. A FMS familial history was reported for 21% of patients.

All efficacy variables showed similar summary statistics between groups at baseline, with mean self-rated scores reflecting:

- severely impaired physical fatigue,
- moderately-to-severely impaired pain, physical health and related quality-of-life, and sleep,
- mildly impaired cognitive performances and anxious feelings,
- and, in accordance with the selection cut-off on BDI, no or minimally impaired depressive mood, mental health and related social and emotional quality-of-life dimensions.

Efficacy Results (1/2)

1/ At the End of the 12-Week 200 mg Daily Fixed Dose Period (Week 16 Time Point) (1/2)

Primary Stepwise Analysis

Milnacipran showed a significant improvement relative to placebo in both:

- the primary composite criterion: placebo and milnacipran responder rates of 14.6% and 24.2%, respectively (odds ratio of 1.9), p=0.0003, and
- the key secondary criterion FIQ-Total score: milnacipran effect *versus* placebo (adjusted mean difference [se]) of –3 (1.2), p=0.015.

Sensitivity Analyses of the Primary Analysis confirmed the robustness of the primary analysis:

- In the PP data set, using LOCF approach with placebo and milnacipran responder rates on the primary criterion of 16.1% and 30.1%, respectively (odds ratio of 2.3), p < 0.0001, and a milnacipran effect *versus* placebo on the FIQ-Total score of –4.3 (1.3), p=0.001;
- In the FAS, using OC approach with placebo and milnacipran responder rates on the primary criterion of 15.7% and 31.3%, respectively (odds ratio of 2.4), p < 0.0001, and a milnacipran effect *versus* placebo on the FIQ-Total score of –4.2 (1.4), p=0.002;
- In the FAS, using BOCF approach, with placebo and milnacipran responder rates on the primary criterion of 13.5% and 23.3%, respectively (odds ratio of 1.97), p = 0.0002; however the milnacipran effect *versus* placebo on the FIQ-Total score using this approach was not significant: -1.7 (1.2), p=0.149;
- In the FAS, using LOCF approach, with no imputation of invalidated pain data and with no invalidation of pain data: results strictly identical to those from the primary analysis.

Influence of Mood and Anxiety on the Primary Composite Criterion

- There was a trend for a treatment*baseline BDI interaction (p=0.103): the lower the baseline BDI, the higher the between-group contrast (for BDI ≤ 10 [n=480]: 14.3% placebo *vs* 25.6% milnacipran responders, BDI ≥ 19 [n=142]: 16% placebo *vs* 20.9% milnacipran-responders);
- There was no treatment*baseline STAI-S or STAI-T interaction (p=0.719 and 0.484, respectively).

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Efficacy Results (2/2)

1/ At the End of the 12-Week 200 mg Daily Fixed Dose Period (Week 16 Time Point) (2/2)

Secondary Analyses of Both Primary Components

The significant improvement on milnacipran *versus* placebo was confirmed for both components of the primary criterion:

- Pain (PED 24h-recall VAS):
  - placebo and milnacipran responder rates of 30% and 38.6%, respectively (odds ratio of 1.5), p=0.007,
  - milnacipran effect *versus* placebo of –4.5 mm, p=0.001 (sensitivity MMRM analysis at V8: -5.1 mm, p=0.0008),
- PGIC:
  - placebo and milnacipran responder rates of 20.6% and 33.3%, respectively (odds ratio of 1.9), p < 0.0001,
  - p < 0.0001 using the Cochran-Mantel-Haenszel (CMH) test on PGIC classes distributions.

Analyses of Secondary Efficacy Variables

All efficacy parameters improved from baseline on average in both groups.

As compared to placebo, milnacipran:

- Demonstrated statistically significant improvements on multiple domains:
  - The improving effect on the main pain variable (PED 24h-recall pain) was confirmed by the statistically significant improvements in all other pain assessments (other PED and Paper weekly-recall, 24h-recall and current pain VAS, brief pain inventory [pain and pain interference], FIQ-Pain VAS and SF-36-Bodily Pain): p values range of 0.014 to < 0.0001,
  - The overall improvement in the patients' condition and functioning (through both the PGIC primary variable and FIQ-Total key secondary variable) was strengthened by the statistically significant improvements in:
    - Quality of life generic (SF-36-Mental and -Physical summary components) and fibromyalgia-specific (FIQ-Total Modified) surveys and most of their dimensions (including Physical Function scores): p values range of 0.04 to 0.001,
    - Fatigue (MFI-Total and most of its dimensions, PED Weekly-recall VAS): p values range of 0.02 to 0.004,
  - Cognitive performances (despite mildly impaired baseline levels): MASQ-Total and its Language dimension improved: p=0.041 and 0.018, respectively,
  - Refreshing sleep: PED Weekly-recall VAS: p=0.007,
- Despite minimally or mildly impaired baseline levels, further improved (non statistically significantly):
  - Depressive feelings: BDI and FIQ-Depression VAS. Consistently, the weekly-recall number of days felt good was borderline statistically significantly increased (*versus* placebo): p=0.083,
  - Anxious feelings STAI-S and FIQ-Anxiety VAS,
  - The remaining cognitive performances (Visual and Verbal Memory, Visual Perception, Concentration),
- Failed to improve most of sleep assessments (except the PED-Weekly-Recall VAS [see above], MOS–Adequacy [both assessing refreshing sleep], MOS-Snoring, and MOS–Daytime Somnolence, that were improved by milnacipran). The only parameter statistically significantly worsened by milnacipran (as compared to placebo) was the MOS-Awakening-Short of Breath-or-With Headache score (p=0.01).

2/ During the treatment Period up to Week 16, most parameters showed a time-dependent within-group increasing improvement profile, and for those parameters that showed statistical and/or numeric significant between-group differences at Week 16, the improving milnacipran effect *versus* placebo was observed as soon as at the first on-treatment assessment visit (Week 4 = end of Dose Escalation), and, for the PED Weekly-Recall (refreshing) Sleep, Pain, and Fatigue VASs (for which the contrasts could be analysed earlier using MMRM), as soon as at Weeks 1, 2, and 3, respectively (p=0.004, 0.0002, and 0.006, respectively).

3/ During the Post-Fixed Dose Period (OC approach), all pain assessments showed:

- from the end of fixed dose, a worsening at the end of down titration, going on at the end of the post-treatment follow-up in both groups,
- At the end of down-titration a still relevant between-group difference in favour of milnacipran,
- At the end of the post-treatment follow-up, better assessments than at baseline in both groups, but no more between-group difference. At the end of the post-treatment follow-up, the responder rate on PGIC was still clinically significantly higher in the Milnacipran group (29%) than in the Placebo group (19.7%).

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Safety Results (1/2)

Adverse Events

A proportion of 74.2% of placebo-treated patients and 84.2% of milnacipran-treated patients reported at least one TEAE. A large majority of TEAEs were of mild or moderate intensity in both groups (93% of TEAEs in both groups). The Investigator did not exclude the relationship with the study drug in 60% and 73% of TEAEs in the Placebo an Milnacipran groups, respectively.

A similar proportion of patients in each group experienced at least one SAE: 16 SAEs were reported for 11 (2.5%) placebo-treated patients, and 14 SAEs for 11 (2.6%) milnacipran-treated patients during the whole study course. Fifteen SAEs in 11 placebo-treated patients and 8 SAEs in 6 milnacipran-treated patients occurred during the 17-week study treatment period. No death was reported during the study course. However, a suicide attempt in a woman of 46 years two months after the last intake of milnacipran resulted in a death. Four SAEs in 2 placebo-treated patients (CPK increased / headache+nausea+vomiting) and 5 SAEs in 3 milnacipran-treated patients (purpura / hypertension+pre-syncope / aneurysm rupture+subarachnoid haemorrhage) had a non-excluded or unassessable relationship with the study drug in the Investigator's opinion.

A higher proportion of patients prematurely withdrew for safety/tolerability reason in the Milnacipran group (22.3%) as compared to the Placebo group (9.9%). AEs that resulted in a definitive treatment discontinuation in the Milnacipran group were mostly hyperhidrosis, headache, tachycardia, and nausea.

The most frequently reported TEAEs in the Milnacipran group and with a significantly higher incidence than in the Placebo group correspond to the well-established safety profile of milnacipran; these were the following:

SOC	PT	Placebo	Milnacipran
Gastro-intestinal system	Nausea	11.2%	26%
	Constipation	2.2%	12.5%
Skin and subcutaneous system	Hyperhidrosis	2.9%	23.7%
Nervous system	Headache	14.8%	20.9%
Cardiac and Vascular systems	Heart rate increased or tachy-cardia	1.4%	10.4%
	Hot flushes	1.1%	7%
Urinary and reproductive systems (considered in male patients only)	Dysuria*	0 male patients	8 (38%) male patients
	Testicular or scrotal pain	0 male patients	4 (19%) male patients

**urinary retention in one case*

It is to be noted that TEAEs coded "blood pressure increased" and "hypertension" were reported in similar (small) proportions of patients in both groups: 4.2% of placebo-treated patients and 5.8% of milnacipran-treated patients.

In both groups, TEAEs mainly occurred during the Dose Escalation phase; this early prevalence was even more evident in the Milnacipran group for vomitings, constipations, hyperhydroses, and hepatic enzymes increases: 77%, 65%, 79%, and 80% of cases, respectively *versus* 47%, 50%, 62%, and 40% of cases in the Placebo group. Furthermore, the 8 dysurias and both of the 2 hypersentivity reactions reported in the Milnacipran group occurred during this phase.

The proportion of severe TEAEs was similar between groups whatever the nature of TEAEs except for hyperhidroses, tachycardiae, and hypertensions that were severe in 10%, 12%, and 8% of cases, respectively in the Milnacipran group, and never in the Placebo group.

Laboratory Tests (1/2)

With respect to **haematology parameters**,

- Time profiles show no relevant differences between groups; a slight trend towards increase in the platelet count was noted at both time points with respective mean (sd) changes in the Placebo and Milnacipran groups of:
  - +1.8 (45) and +11.7 (35) G/L at V5-Week 4, and
  - –4.0 (38) and +16.3 (35) G/L at V8-Week 16/PW,
- There were no relevant between-group differences in PCA incidences for this parameter and all other haematology parameters,

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

Safety Results (2/2)

Laboratory Tests (2/2)

- Haematological CNALVs were only found for neutropenia, and were more frequent in the Placebo group (9 *vs* 3 in the Milnacipran group);

With respect to **biochemistry parameters**,

- Time profiles showed no relevant differences between groups; a slight trend towards increase in the hepatic enzymes was noted in the Milnacipran group at V8-Week 16/PW (and at V5-Week 4 for PAL), with the following mean (sd) changes at that time point in the Placebo and Milnacipran groups, respectively:
  - 0 (5.5) and +1.4 (6) U/l for ASAT,
  - -0.5 (9) and +1.8 (11) U/l for ALAT,
  - -1 (13) and +2.7 (13) U/l for GGT,
  - -2.3 (10) and +4.5 (10) U/L at V8 for PAL (and -1.3 (8) and +4 (12) U/l at V5);
- There were no relevant between-group differences in PCA incidences parameters except for ALAT increases that were more frequent at both time points in the Milnacipran group (2.5% at both time points) than in the Placebo group (0.7% at V5, and 0.5% at V8) and for GGT increases more frequent at V8 in the Milnacipran group (2%) than in the Placebo group (0.7%);
- There were no relevant between-group differences in CNALV incidences. All CNALVs but one were found for ALAT (3 and 4 in the Placebo and Milnacipran groups, respectively); the remaining CNALV was found for ALP in the Milnacipran group. All CNALVs with further controls available were reversible except one ALAT value at V8 in a milnacipran-treated patient, aggravated at V9 and V10.

Vital Signs

Mean profiles over time show trends towards increase on milnacipran for the three vital sign parameters: mean increases from baseline by 0-2.3 mmHg for SBP, 2.8-3.9 mmHg for DBP, and 7.7-10.6 bpm for HR. At the end of the 2-week post-treatment period, vital sign values had returned (blood pressure) or almost returned (HR: mean increase from baseline by +3 bpm) to baseline levels.

Consistently, there were higher incidences of PCs towards increase for the three parameters in the Milnacipran group than in the Placebo group, and more specifically for HR. Incidences of SBP, DBP, and HR PCs towards increase were respectively of about: 17%, 14%, and 20% in the Placebo group and of 30%, 27%, and 58% in the Milnacipran group.

Very few of these PCs were CSCs in both groups, and corresponding incidences were no more relevantly different between groups. Incidences of SBP, DBP, and HR CSCs towards increase were respectively of: 1.1%, 2.0%, and 0.2% in the Placebo group and of 0.9%, 3.5%, and 1.4% in the Milnacipran group.

ECG

There was no indication of QTc (Fridericia correction) prolongation on milnacipran.

A similar proportion of patients presented treatment-emergent ECG abnormalities in the Cardiologist's opinion: 20 and 22.5% in the Placebo and Milnacipran groups, respectively. Sinusal tachycardiae > 100 bpm were more frequent in the Milnacipran group (5.8% *vs* 0.7%) while sinusal bradycardiae < 50 bpm and 1st degree auriculo-ventricular blocks were more frequent in the Placebo group (2.7% *vs* 0.7% and 3.1% *vs* 0.2%, respectively).

Conclusion

The trial results consistently confirm that milnacipran 200 mg daily for up to 12 weeks is a safe and effective treatment of FMS, with siginificant effect on various key components of the syndrome. The study treatment significantly improved not only widespread pain and Patient Global status but also multiple core symptoms of the syndrome including fatigue, health-related physical and mental quality of life, non-refreshing sleep, and cognitive complaints. Milnacipran effect was rapid (as soon as at Week 2 for pain). These results define the efficacy spectrum of milnacipran. The beneficial effects of milnacipran in FMS seem to be independent from the drug antidepressant effect. No unexpected tolerability/safety concerns were reported on milnacipran.

Date of Report: 5 May 2008