**Pierre Fabre Médicament**
**Represented by: Institut de Recherche Pierre Fabre**
**45, Place Abel Gance**
**F-92654 Boulogne Cedex**

# 1. TITLE PAGE

# CLINICAL STUDY REPORT

**The Effect of Milnacipran 100 mg *b.i.d.* on Sensitivity to Stimulus-Evoked Pain in Patients with Fibromyalgia: a fMRI Neuroimaging Study**

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| **Investigational Product**: | Milnacipran 100 mg *b.i.d.* |
| **Study Design**: | Multicentre, 13-week, randomised, placebo-controlled |
| **Protocol Number**: | F02207 GE 2 04 |
| **Phase of Development**: | II |
| **Date of First Enrolment**: | 21 October 2005 |
| **Date of Last Completed**: | 26 April 2007 |
| **Coordinator**: | Ernest Choy, MD<br>*King's College Hospital - London SE5 9RJ - UK*<br>*Tel: +(44) 207 848 5125 / Fax: +(44) 207 848 5202* |
| **Sponsor Representatives for Study Report**: | **Project Clinical Manager**: Yves Mainguy, MD<br>*Tel: +(33) 5 62 24 27 40 / Fax: +(33) 5 62 24 54 30*<br>**Study Statistician**: Mélanie Groc<br>*Tel: +(33) 5 62 24 27 89 / Fax: +(33) 5 62 24 54 31*<br>**Medical Writer**: Agnès Montagne, MD<br>*Tel: +(33) 5 62 24 27 38 / Fax: +(33) 5 62 24 54 30* |
| **Date of Report**: | 28 April 2008 |

Study performed in compliance with Good Clinical Practice.

# 2. SYNOPSIS

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| **Name of Company: Pierre Fabre Médicament** | **Individual Study Table** | **(For National Authority Use Only)** |
| **Name of Finished Product: F2207 FMS** | **Referring to Module 5 of the Dossier** | |
| **Name of Active Substance: milnacipran hydrochloride** | **Vol.: .....Page: .....** | |

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| **Title of Study:** | The Effect of Milnacipran 100 mg *b.i.d.* on Sensitivity to Stimulus-Evoked Pain in Patients with Fibromyalgia: A fMRI Neuroimaging Study | |
| **Investigators:** | - United Kingdom (UK): Dr Ernest Choy (Coordinating Investigator, Principal Investigator), Dr Louise Pollard (Clinical Investigator), Prof. Steven Williams (fMRI Investigator),<br>- Sweden: Prof. Martin Ingvar (Principal Investigator), Dr Eva Kosek (Clinical Investigator), Karin Jensen (fMRI Investigator),<br>- Germany: Dr Thorsten Giesecke (Principal Investigator and fMRI Investigator until Mar 2006), Dr Frank Petzke (Clinical and fMRI Investigator, Principal Investigator from Mar 2006), Dr Hanke Marcus (Clinical and fMRI Investigator). | |
| **Study Centres:** | - Centre no.1: King's College Hospital, Rheumatology Department, Clinical Trials Unit, London SE5-9RJ- UK,<br>- Centre no.2: Karolinska Hospital, Neurosciences Department, MR Research Centre, 17176 Stockholm - Sweden,<br>- Centre no.3: University Hospital, Anaesthesiology Department, 50924 Cologne - Germany. | |
| **Publication (reference):** | N/A | |
| **Study Period:**<br>**Date of First Enrolment**<br>**Date of Last Completed** | 18 months<br>21 Oct 2005<br>26 Apr 2007 | **Phase of development:** II |
| **Objectives:**<br>**Primary:** | To assess the effect of 12 weeks of treatment with milnacipran on sensitivity to stimulus-evoked pain in outpatients with fibromyalgia syndrome. | |
| **Secondary:** | - To assess the correlation between the effect of milnacipran on sensitivity to stimulus-evoked pain and findings on functional Magnetic Resonance Imaging (fMRI),<br>- To determine whether the study patients could be categorised into clusters based on baseline measurements and evaluate whether response to treatment differs within clusters,<br>- To assess the safety and tolerability of 13 weeks of treatment with milnacipran. | |
| **Methodology:** | 13-week, multicentre, double-blind, placebo-controlled, randomised, 2-parallel group trial.<br>Eight scheduled assessment visits: Screening Visit - V1 (Day -28 to Day -7); V2 (Day -1): Baseline Stimulus-Evoked Pain Response (S-R), Randomisation Visit - V3 (Day 1): Baseline fMRI Scan; V4 (Week 3); V5 (Week 7); V6 (Week 12): On-Treatment S-R; V7 (Week 12 [+1 day]): On-Treatment fMRI Scan; End-of-Study Visit - V8 (Week 13 [+2 days]). | |
| **Number of Patients:** | 92 randomised and treated patients: 46/milnacipran, 46/placebo. | |
| **Diagnosis and Main Criteria for Inclusion:** | - Female patients with fibromyalgia according to the 1990 ACR criteria,<br>- Aged 18 to 55 years,<br>- Right-handed,<br>- With no childbearing potential or using a medically acceptable form of contraception for at least two months before inclusion,<br>- Willing to withdraw from CNS-active drugs commonly used for FMS (including anti-depressants, anti-convulsants, mood stabilizers, opioids, narcotic patches) or from other therapies such as transcutaneous electrical nerve stimulation, biofeedback, tender and trigger point injections, acupuncture, and anaesthetics,<br>- With a Weekly-Recall Pain intensity rated at least 40 on a 100-mm VAS at randomisation. | |

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| **Test Product,** | Milnacipran capsules, 25 mg and 50 mg, |
| **Dose,** | **3-week Dose Escalation Phase:**<br>Step 1: 25 mg/d 2 days 25 mg pm<br>Step 2: 50 mg/d 5 days 25 mg am and 25 mg pm<br>Step 3: 100 mg/d 7 days 50 mg am and 50 mg pm<br>Step 4: 200 mg/d 7 days 100 mg am and 100 mg pm<br>**9-week Fixed Dose Phase:**<br>Step 5: **200 mg/d** **9 weeks** **100 mg am and 100 mg pm**<br>**9-day Down-Titration Phase**:<br>Step 6: 100 mg/d 3 days 50 mg am and 50 mg pm<br>Step 7 50 mg/d 3 days 25 mg am and 25 mg pm<br>Step 8 no treatment 3 days, |
| **Mode of Administration,** | Oral, *b.i.d.* (apart from step 1), morning and evening during meals, |
| **Batch Numbers:** | SB0295 and SB0227 for 25 mg and 50 mg milnacipran capsules, respectively. |
| **Duration of Treatment:** | 13 weeks |
| **Control Therapy,** | Placebo capsules matching milnacipran capsules, |
| **Dose and Mode of Administration,** | Identical to milnacipran dose and mode of administration, |
| **Batch Numbers:** | SB0329 and SB0228 for placebo capsules matching 25 mg and 50 mg milnacipran capsules, respectively. |
| **Criteria for Evaluation (1/2):** | **Efficacy:**<br>***Primary Variable***<br>Pressure pain sensitivity (subjective VAS assessment) to multiple (15) pressure stimuli of supra-threshold intensities applied (randomly) to the left thumb: Screening (familiarisation), Day -1 and Week 12.<br>- Primary criterion = stimulus-response (S-R) curve at Week 12/PW,<br>- Derived measure = P50 (pressure for a 50-mm VAS)<br>***Secondary Variables***<br>- CNS activation pattern (fMRI): Baseline, Week 12,<br>- Weekly-recall pain VAS Baseline, Weeks 3, 7, 12, 13,<br>- Current pain VAS: Baseline, Weeks 3, 7, 12, 13,<br>- Pain drawing: Baseline, Week 12,<br>- Tender point count: Baseline, Week 12,<br>- Pressure pain threshold (PPT): Baseline, Week 12,<br>- Patient Global Impression of Change (PGIC): Week 12,<br>- Short form McGill Pain Questionnaire (SF-MPQ): Baseline, Week 12,<br>- Short form 36 (SF-36): physical & mental scores (PCS and MCS) Baseline, Week 12,<br>- Fibromyalgia Impact Questionnaire (FIQ): Total score and physical function subscore: Baseline, Week 12,<br>- Chalder Fatigue Scale (CFS): Baseline, Week 12,<br>- Pittsburg Sleep Quality Index (PSQI): Baseline, Week 12,<br>- Coping Strategies Questionnaire (CSQ): Baseline,<br>- Swedish Universities Scales of Personality (SSP): Baseline,<br>- Beck's Depression Inventory (BDI): Baseline,<br>- State-Trait Anxiety Inventory:<br>• State Specification (STAI-S): Baseline, Week 12,<br>• Trait Specification (STAI-T): Baseline |

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**Criteria for Evaluation (2/2):**

**Safety:**

- Adverse events (AEs) and concomitant treatments: continuous assessment
- Lab Tests (i/ haematology: red blood cell count, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, white blood cell count including differential, platelet count, prothrombin time, activated partial thromboplastin time, international normalized ratio; ii/ biochemistry: sodium, potassium, chloride, calcium, phosphate, random glucose, urea, creatinine, alkaline phosphatase, total bilirubin, aspartate amino-transferase, alanine amino-transferase, total protein and albumin, thyroid-stimulating hormone, and thyroxine): Baseline, Weeks 3, 12
- Vital Signs (systolic / diastolic blood pressure [SBP / DBP], heart rate [HR]) and Weight: Baseline, Weeks 3, 7, 12, 13,
- General Physical Exam: Baseline, Weeks 12, 13,
- ECG: Baseline, Weeks 3, 12.

**Statistical Methods (1/3)**

**Clustering**

- On the Cluster Data Set *i.e,* "Without Major Protocol Deviation before or at Randomisation, and Complete Case at Baseline on Reduced* Assessments: Pain Pressure Tolerance Threshold, SF-MPQ, SF-36-PCS, SF-36-MCS, BDI, STAI-T, STAI-S, PSQI, CSQ-Catastrophizing, SSP-Somatic Trait Anxiety, -Psychic Trait Anxiety (**: removal of variables creating noise*);
- Ward's hierarchical clustering method; determination of clusters by observing the corresponding dendrograms. Sensitivity analyses: using average, single, and complete linkage methods; Ward's method repeated on the principle components. Exploratory analysis on screened patients,
- Summary statistics on Baseline data of clusters.

**Efficacy (1/2)**

***Primary Analysis of the Primary Criterion (S-R curve at Week 12/PW)***

- On the Full Analysis Set (FAS) *i.e.*, patients having received at least one dose of study treatment, and with at least one post-baseline evaluation of an efficacy criterion,
- Mean profile of S-R curves at Week 12/PW estimated using a polynomial regression model with: Pressure and Pressure$^2$ as linear and quadratic components, Treatment and Centre as fixed factors, Treatment*Pressure and Treatment*Pressure$^2$ as interaction terms, Baseline P50 as covariate, and Patient as random factor,
- Treatment effect quantified by the between-group difference on the VAS at Week 12/PW (if no P*T and P$^2$*T interaction [*i.e.*, no difference on slopes and curvatures of S-R curves]).

***Supportive Analysis of the Primary Analysis***

Primary analysis repeated on the per-protocol (PP) data set (*i.e,* FAS patients having reached the end of the dose escalation, with a complete evaluation of the primary efficacy criterion, and without any major deviation).

***Additional Analyses of the Primary Criterion and Derived Measures (1/2)***

- Primary analysis repeated on the FAS, using the baseline-observation-carried-forward (*BOCF*) imputation of missing data;
- *Responder Analysis*: Cochran-Mantel-Haenszel (CMH) stratified by Centre on % of responders at Week 12/PW (responder = Week 12-VAS values < Day –1-VAS values at least in the interval of the 2 highest Week 12-pressures, *and* Week 12-P50 ≥ Day –1-P50);
- *ANCOVA on P50 change* from baseline (Day-1) to Week 12/PW, with Treatment and Centre as main effects and Baseline P50 as covariate;

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**Statistical Methods (2/3)**

**Efficacy (2/2)**

***Additional Analyses of the Primary Criterion and Derived Measures (2/2)***

- *Regression of P50 change from baseline to Week 12 on Clusters*:
  - On the FAS-Cluster Subset (see "Clustering"),
  - Multiple imputation (MI) and LOCF imputation of missing data,
  - Multiple regression model with: baseline value, cluster, treatment, and cluster*treatment interaction,
  - Sensitivity analyses:
  - - Treatment effect adjusted by fixed covariate clusters and treatment*cluster interactions where significant, adjusted in separate models by centre and treatment*centre interactions where significant, concomitant treatment intake, points of influence and outliers,
  - - Main model repeated on the PP-Cluster and Complete Case data sets
  - Exploratory analysis using a stepwise model fitting all baseline variables deemed to be potential predictors.
- *Influence of Centre and Baseline Characteristics on the Primary Criterion*.

***Analyses of Secondary Criteria (1/2)***

- *fMRI Analysis*:
  - On the fMRI data set (having completed 10 weeks of study treatment, having received ≥ 50% of treatment, having had ≥ 1 intact fMRI sequence available at baseline and W12/PW),
  - General linear models including within-patient and between-patient variances on the drug effect to similar stimulus conditions, Bonferroni-like adjustment for multiple comparisons,
  - Within-group represetation of brain activity assessed by using a one sample t-test,
  - Between-group contrasts assessed by using 2x2 ANOVA.
- *Systematic Analyses of Non-fMRI Secondary Efficacy Measures:*
  - On the FAS,
  - ANCOVA with Treatment and Centre as main effects and Baseline Value as covariate on quantitative data, and CMH test stratified by Centre on categorical data (except use of rescue medications: descriptive analysis [N (%) of patients by study periods and classes of duration of use),
  - Descriptive statistics on values and changes over time;
- *Additional Analyses of Non-fMRI Secondary Efficacy Measures:*
  - Predictor analysis for overall PPT outcome,
  - Mixed-Effect Model for Repeated Measures (MMRM) on Current and Weekly-Recall Pain VASs changes over time,
  - PGIC Responder (scored "1" or "2") analysis,
  - Cluster Predictor Analysis for SF-MPQ (change from baseline to W12): cf for P50.

**Safety (1/2)**

On the Safety Data Set (= All Patient Treated data set),

***Length of Exposure:*** summary statistics for global exposure, n (%) of patients by range of exposure: < 21, 21-70, 70-83,and > 83 days,

***AEs (1/2)*:**

- N (%) of patients: with at least one: AE, treatment-emergent AE (TEAE), serious AE (SAE), AE leading to premature withdrawal (PW), TEAE with "associated" relationship to study drug,

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**Statistical Methods (3/3):** **Safety (2/2)**

***AEs (2/2)*:**

- N (%) of patients with at least one TEAE by System Organ Class (SOC) and Preferred Term (PT) of MedDRA, max. intensity, most severe relationship to study drug,
- Tabulated individual data for SAEs and AEs leading to PW;

***Lab Tests*:**

- Descriptive statistics for values and changes over time,
- N (%) of patients with potentially clinically significant changes,
- Scatter plots as a function of baseline values for W3 and W12/PW values,
- Tabulated individual data for clinically noteworthy abnormal lab values (CNALV);

***Vital Signs*:**

- Descriptive statistics for values and changes over time, graphics of mean profiles,
- N (%) of patients with: i) predefined potentially clinically significant changes (PC), ii) PC leading to predefined potentially clinically significant values (CSC), iii) predefined orthostatic hypotension;

***Weight***: Descriptive statistics for values and changes over time;

***Physical Exam*:** Number of changes of general physical status (normal/abnormal) over time;

***ECG*:**

- Number of changes in the Cardiologist's assessment (sinusal/non sinusal rhythm and normal/abnormal ECG) over time,
- 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 1 and ATC 2 classes.

**Summary – Conclusions (1/2)**

**Patients (1/2)**

***Disposition and Demographics (1/2)***

157 patients were screened (36, 56, and 65 in the UK, German and Swedish centres, respectively).

Of them, 92 (58.6%) were randomised (19 [52.8%], 36 [64.3%], and 37 [56.9%] in the UK, German and Swedish centres, respectively). All randomised patients received at least one dose of study treatment. The patient disposition from randomisation to study completion was the following (several reasons may have led to a PW):

| | Placebo | Milnacipran | Total |
|---|---|---|---|
| **Randomised** | **46** | **46** | **92** |
| ***Withdrawn (all)*** | ***8 (17.4%)*** | ***14 (30.4%)*** | ***22 (23.9%)*** |
| - *Adverse event* | *4 (8.7%)* | *11 (23.9%)* | *15 (16.3%)* |
| - *Therapeutic failure* | *5 (10.9%)* | *3 (6.5%)* | *8 (8.7%)* |
| - *Patient's decision* | *4 (8.7%)* | *4 (8.7%)* | *8 (8.7%)* |
| - *Investigator's decision* | - | *2 (4.3%)* | *2 (2.2%)* |
| **Completers** | **38 (82.6%)** | **32 (69.6%)** | **70 (76.1%)** |

There was no loss to follow-up.

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**Summary – Conclusions (2/2)**

**Patients (2/2)**

***Disposition and Demographics (1/2)***

The patient disposition across the different data sets analysed was well balanced between treatment groups:

| | Placebo | Milnacipran | Total |
|---|---|---|---|
| **Treated (Safety Data Set)** | **46** | **46** | **92** |
| **FAS** | **45** | **45** | **90*** |
| **PP Data Set** | **37** | **34** | **71** |
| **Cluster Data Set** | **43** | **40** | **83** |
| **fMRI Data Set** | **32** | **32** | **64** |

**Of them, 74 (38 and 36 in the Placebo and Milnacipran groups, respectively) had their post-baseline S-R assessment*

Treatment groups were homogeneous with respect to demographics. All treated patients were women with mean (sd): age of 44.2 (8.2) years), BMI of 26.3 (4.6) kg/m$^2$ (23.6% of obese persons), tenderness duration of 11.1 (7.9) years, and truely diagnosed FMS of 4.5 (3.9) years.

***Clustering***

Three clusters emerged from Ward's linkage with the following characteristics:

- ***Cluster 1*** (n=45) had an intermediate mental functioning, the **worst physical functioning** (lowest SF-36 PCS mean score), an intermediate spontaneous pain sensitivity and the **highest evoked pain sensitivity** (lowest mean pain tolerance threshold),
- ***Cluster 2*** (n=16) had the **worst mental functioning** (poorest related QoL, bad mood, high anxiety, and catastrophizing levels, poorest quality of sleep); a moderately impaired physical functioning, the **highest spontaneous pain sensitivity** (highest mean SF-MPQ score) and the **lowest evoked pain sensitivity**,
- ***Cluster 3*** (n=22) had the **best mental functioning** (close to normal US population) **and physical functioning**; these patients showed the **lowest spontaneous pain sensitivity** and an intermediate evoked pain sensitivity.

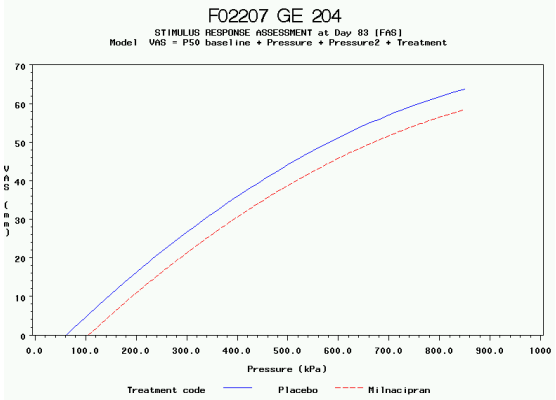
**Efficacy Results (1/2)**

***Primary Criterion: S-R Curve at Week 12***

The quasi similarity between groups at baseline of the adjusted mean S-R curves (p = 0.81) with no randomisation effect on slope or curvature allows a reliable interpretation of the primary criterion.

At Week 12, there was a **5.2-mm VAS downward shift of the Milnacipran mean S-R curve from the Placebo curve** over the entire panel of applied pressures *i.e.*, from pain threshold to pain tolerance threshold (**p=0.11**).

Considering the exploratory nature of the trial (not powered to detect a difference) and the relative small analysable sample size (n = 74), this result is compatible with a clinically relevant effect of milnacipran in decreasing FMS patients' sensitivity to evoked pain. The comparable results in the PP data set (4.8-mm downward shift, p = 0.13) confirm the robustness of the primary analysis.



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**Efficacy Results (2/2)**

***Additional analyses on the primary criterion derived measures at Week 12***, corroborate the primary analysis findings (*i.e.*, a clinically relevant milnacipran effect):

- A 15% higher proportion of responders on S-R curve in the Milnacipran group (57.1%) than in the Placebo group (42.1%), p=0.24,
- A 41.9 kPa adjusted higher mean increase in P50 from baseline in the Milnacipran group (+96.3 kPa) than in the Placebo group (+54.4 kPa), p=0.37.

The milnacipran S-R response was shown to be significantly influenced by the baseline sensitivity level (**p<0.001 in patients with P50-Baseline > 450 kPa** [*i.e.*, lowest pain pressure sensitivity]).

***Regression of P50 change at Week 12 on clusters:***

Main regression analysis shows an increased milnacipran effect in Cluster 3 and at a lesser degree in Cluster 2, with (LOCF approach): a mean increase in P50 from baseline:

- in milnacipran-treated patients of Cluster 3 of +189.8 kPa vs +35.8 kPa in placebo-treated patients of Cluster 3 (mean between-group difference of +157.6 kPa, p=0.052),
- in milnacipran-treated patients of Cluster 2 of +103.6 kPa vs –46.8 kPa in placebo-treated patients of Cluster 2 (mean between-group difference of +160.3 kPa, p=0.098),

Sensitivity analyses of the main regression analysis notably reveal a greater and significant milnacipran effect:

- in **PP patients of Cluster 3: mean between-group difference of +197.9 kPa, p=0.025**.
- and, due to high baseline P50 values, in the **Cologne Centre: mean between-group difference of +248.6 kPa, p<0.001**.

***Secondary Non-fMRI Variables***

Almost all secondary efficacy variables showed similar summary statistics between groups at baseline and improved on average in both groups after 12 weeks of treatment;

The between-group differences in change from baseline showed non significant trends in favour of milnacipran on a number of variables. The most relevant mean between-group differences (≥ 10% change difference) were (adj. LS mean difference, p value):

- Among other pain variables:
  - Quadriceps paired site PPT (+51.1 kPa, p=0.24),
  - Current Pain VAS (–5.5 mm, p=0.28),
- Among health-related QoL variables:
  - Role Physical and Vitality SF-36 scores (+3.72 and +3.96, p=0.45 and 0.37, respectively),
  - **General Health SF-36 score (+7.0, p=0.023),**
- Depression FIQ item VAS (–5.78 mm, p=0.38),
- Sleep Medication Use PSQI score (-0.3, p=0.24).

***fMRI***

The procedure used for measurements of pain-evoked brain activity during fMRI was validated by reproducing the pain-matrix previously described in the literature, including the periaqueductal grey, amygdala, S1, S2, anterior cingulate cortex and insula.

The Milnacipran group exhibited increased activity in 9 brain regions after treatment as compared to before treatment. The Placebo group only exhibited increased activity in 2 regions after treatment. Several regions with increased activity in the Milnacipran group are implicated in the descending pain inhibitory network which was not found in the Placebo group. No regions displayed greater cerebral activity before treatment as compared to after treatment in any of the groups.

Between-group contrasts showed that brain activity in the posterior cingulum and precuneus was significantly greater after treatment in the Milnacipran group as compared to the Placebo group (p<0.05, uncorrected). Increased activity of the posterior cingulum has previously been reported after treatment in chronic pain patients.

With respect to the treatment effect on accumulated pain (temporal summation), comparing brain activity during the first and last sequence, following treatment, the Milnacipran group exhibited greater activity than the Placebo group in the thalamus (p=0.057), a region in which non-treated FMS patients have previously shown decreased basal and pain-evoked activity in comparison to healthy control subjects.

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**Safety Results**

***Adverse Events***

Forty (87%) placebo-treated patients and 45 (97.8%) milnacipran-treated patients reported at least one TEAE. A large majority of TEAEs were of mild or moderate intensity in both groups (97.5% and 92.9% in the Placebo and Milnacipran groups, respectively).

Eight SAEs were reported in two placebo-treated patients (myocardial infarction / worsening of FMS pain) and four milnacipran-treated patients (breast cancer / meniscus lesion / diverticulitis / endometriosis then gastric ulcer associated with anaemia). All of these SAEs were considered non related to the study drug by both the Investigator and the Sponsor,

The proportion of patients who prematurely withdrew for safety/tolerability reason was 8.7% and 23.9% in the Placebo and Milnacipran groups, respectively. In the Milnacipran group, AEs that resulted in a premature withdrawal were mostly gastro-intestinal disorders (15.7% of milnacipran-treated patients) that almost all occurred during the dose escalation phase.

The most frequently reported AEs in the Milnacipran group and with a higher incidence than in the Placebo group correspond to the well-established safety profile of milnacipran in other indications such as depression; these were in the:

- Gastro-Intestinal system: nausea (50% *vs* 30%), vomiting (26% *vs* 4%), and upper abdominal pain (15% *vs* 6.5%),
- Nervous system: headache (46% *vs* 33%),
- Cardiac and Vascular systems: AEs coded as or related to an increased blood pressure (44% *vs* 11%), AEs coded as or related to an increased heart rate (22% *vs* 4%),
- Skin and Subcutaneous system: hyperhidrosis (17% *vs* 2%).

These AE profiles are charateristic of the population studied (fibromyalgic female patients): high incidence of fibromyalgia-related symptoms such as nausea and headache in both groups, and no milnacipran impact on the urinary system (absence of dysuria).

***Laboratory Tests***

For all laboratory parameters, there were no differences between groups in terms of profiles over time, and individual (potentially) clinically significant changes and values.

***Vital Signs***

Vital sign time profiles and individual data show:

- No relevant findings with respect to SBP,
- Trends towards increase in DBP and HR in the Milnacipran group, all over the study course, with a maximum average increase from baseline by 7 mmHg at Week 7 for DBP, and 13.5 bpm at Week 12 for HR. At the end of the Down-Titration phase, DBP values had almost returned to baseline values on average, while HR values had decreased but were still increased from baseline on average (by 6 bpm). Consistently, potentially clinically significant increases were more frequent in the Milnacipran group for both parameters: 35% *vs* 13% for DBP and 61% *vs* 4% for HR. Three of these increases, in DBP only, led to a potentially clinically significant values that did not exceed 108 mmHg.

***ECG***

- There was no indication of $QT_{CF}$ prolongation on milnacipran,
- A sinus tachycardia was reported by the Cardiologist in two milnacipran-treated patients.

**Conclusion**

This exploratory mechanistic study demonstrated the value and potential of using more objective methods to assess a response to treatment in FMS clinical trials. In this small-sized study, conventional patient-reported outcome measures would not be expected to show a statistically significant difference, yet pressure pain assessment using stimulus response curves and fMRI showed substantial and, in the case of fMRI, statistically significant differences in favour of milnacipran as compared to placebo. Treatment with milnacipran alters cerebral activity evoked by painful pressure in brain regions known to be involved in pain modulation. Cluster analyses and analyses of baseline sensitivity are consistent with the demonstration in previous reports of subgroups that may respond differentially to specific treatments. No unexpected tolerability/safety concerns were reported for milnacipran. The result of this study supports the positive therapeutic findings of pivotal phase III trials.

**Date of Report: 28 April 2008**

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