**Pierre Fabre Médicament**
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**45, Place Abel Gance**
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# 1. TITLE PAGE

# ABRIDGED CLINICAL STUDY REPORT

**Proof of Concept study of the efficacy and tolerability of a 4-week treatment with F13640 in patients in whom the adaptation of opioid therapy of cancer pain has failed.**

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| **Investigational product**: | F13640: capsules 0.5 mg |
| **Study Design**: | A prospective, multinational, multicentre, randomised, double-blind, placebo-controlled study |
| **Protocol number**:<br>**EudraCT number:** | F13640 GE 2 09<br>2007-003249-34 |
| **Phase of development**: | II |
| **Date of first enrolment**: | March 20, 2008 |
| **Date of last completed**: | November 3, 2008 |
| **Co-ordinator**: | Philippe POULAIN, MD<br>Institut Gustave Roussy<br>39, rue Camille Desmoulins, F-94805 Villejuif Cedex |
| **Sponsor Representatives for study report**: | Clinical Programs Director: L. Mansuy - *[+ 33(0)5 62 24 27 11]*<br>Clinical Trial Director: MT. Pétrissans - *[+33(0)5 62 24 27 57]*<br>Statistician: S. Gautier - *[+33(0)5 62 24 54.21]*<br>Medical Writer: C. Goulesque - *[+33(0)5 62 24 27 45]* |
| **Date of report**: | **May 18, 2010** |

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:** | **Referring to Module 5 of the Dossier** | |
| **Name of active substance** *(or ingredient)***: F13640** | **Vol.: .....Page: .....** | |

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| **Title of study:** | Proof of Concept study of the efficacy and tolerability of a 4-week treatment with F13640 in patients in whom the adaptation of opioid therapy of cancer pain has failed. | |
| **Coordinating Investigator:** | Philippe Poulain, MD (Institut Gustave Roussy) | |
| **Investigators:** | Investigators in 7 oncology centres of 5 countries (Belgium, Czech Republic, France, Hungary, Italy) | |
| **Study centres:** | 7 centres recruited 8 patients: 3 centres in France, 1 in Belgium, 1 in Italy, 1 in Czech Republic recruited 1 patient each, and 1 centre in Hungary recruited 2 patients. | |
| **Publication (reference):** | NA | |
| **Studied period:** | 8 months | **Phase of development: II** |
| **(date of first enrolment)** | March 20, 2008 | |
| **(date of last completed)** | November 3, 2008 | |
| **Objectives:** | **Primary objective**:<br>- To study the enhancement of analgesia by F13640 (up to 2 mg/day) when gradually introduced in combination with opioid treatment after 14 days evaluated by the percentage of responders in patients who have failed adaptation of opioid therapy for cancer pain, when administered for 2 weeks including a 7-day titration period.<br>**Secondary objectives**:<br>- To evaluate if F13640 treatment allowed decreasing cumulative opioid consumption (opioid saving) and reducing adverse effects whatever the dose administered during the treatment period,<br>- To evaluate if F13640 induced a long lasting analgesic effect after the treatment period and F13640 withdrawal could cause any rebound effect.<br>- To assess pain relief, impact on sleep, safety and tolerability on this population during the study period.<br>**None of these objectives were evaluated, as no planned analysis was performed due to the low number of treated patients (7) at the Sponsor's decision of premature end of this study due to strategic reasons.** | |
| **Methodology:** | Prospective, multinational, multicentre, randomised, double-blind, placebo-controlled study on 2 parallel groups (F13640 and placebo), 4-weeks randomised treatment including a progressive titration over the first 7 days (= phases A + B) and followed by a 10-day placebo-period (phase C).<br>- Selection period (7 days minimum and 28 days maximum): wash-out period for prohibited treatments (if applicable) with prior opioid analgesic treatment maintained unchanged,<br>- Phase A (14 days): prior opioid analgesic treatment maintained unchanged, study drug added,<br>- Phase B (14 days): progessive decrease of prior opioid analgesic treatment, continuation of study drug,<br>- Phase C (10 days): follow-up placebo period, single blind for both groups. | |
| **Number of patients:** | 72 patients were planned.<br>From the 14 selected patients, 8 were randomised and 7 were treated in this study, 5 in the F13640 group and 2 in the placebo group. | |

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| **Diagnosis and main criteria for inclusion:** | - Patient having signed the informed consent<br>- Affiliate to the social security system or equivalent as applicable in the national regulation<br>- Patient able and willing to use the PDA device daily for the duration of the study<br>- Out-patient male or female,<br>- Aged ≥ 18 years and ≤ 65 years,<br>- Diagnosis of cancer confirmed,<br>- Life expectancy ≥ 3 months,<br>- With cancer pain for more than one month,<br>- Under fixed scheduled opioid treatment (oxycodone, morphine, hydromorphone, or fentanyl only) <u>for cancer pain</u> for at least 7 days before inclusion,<br>- In failure of opioid therapy adaptation (oxycodone, morphine, hydromorphone or fentanyl only): 24-hour recall pain intensity score ≥ 40mm on a 0-100mm Visual Analogue Scale (VAS rest or mobilization) at the selection visit, in spite of appropriate oral or transdermal opioid treatment at the maximum tolerated dose, where any adjunctive analgesic medication had been instituted before, such treatment was continued in an unchanged manner:<br>- Average 24-hour recall pain intensity score of the last 7 days before inclusion ≥ 40 on a 0-100 Visual Analogue Scale on a Personal Digital Assistant,<br>- Record of at least 4 assessable evaluations of the 24-hour recall pain intensity score in the Patient Digital Assistant over the 7 days preceding the inclusion,<br>- Chemotherapy protocol not modified within the 4 weeks period preceding Day 1<br>- In case of chemotherapy protocol on-going, the patient had received at least 2 chemotherapy cycles before selection,<br>- AST/SGOT and ALT/SGPT less than 4 times the upper normal value<br>- Normal or considered as not clinically significant other laboratory safety tests and ECG parameters, on the Investigator's opinion and according to CTC grading (grade I and grade II included) |
| **Test product,** | F13640: 0.5 mg capsules |
| **Doses,** | 0.5 mg/day, 1 mg/day, 1.5 mg/day and 2 mg/day. |
| **Mode of administration,** | Oral administration [0.5 mg/day (*o.d.*), 1 mg/day (0.5 mg *b.i.d.*) 1.5 mg/day (1x0.5 mg morning and 2x0.5 mg evening) and 2 mg/day].<br>Titration : 2-day step-up dose regime period:<br>- from 0.5 mg/day up to 1 mg/day, the dose was increased to next dose level according to tolerability,<br>- from 1 mg/day up to 2mg/day, the dose was either increased to the next dose level, decreased to the previous dose level or maintained at the same dose level according to efficacy and tolerability. |
| **Batch number:** | Batch number CFS 172, Expiry date: 12-2008 (Therapeutic Units 1001 to 1072)<br>Batch number CFS 183, Expiry date: 04-2009 (Therapeutic Units 1073 to 1144) |
| **Duration of treatment:** | Randomised period: 4-weeks including a 7-day titration period (D1 to D28)<br>Follow-up placebo period: 10 days (D29 to D38) |

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| **Reference therapy,** | Placebo matching F13640 capsules |
| **Doses, Mode of administration,** | Placebo was administered in the same conditions as the test product during phases A and B and for both groups in single blind during phase C (follow-up period) |
| **Batch number:** | Batch number CFS 171, Expiry date: 06-2011 (Therapeutic Units 1001 to 1072)<br>Batch number CFS 182, Expiry date: 10-2011(Therapeutic Units 1073 to 1144) |
| **Others, Doses, Mode of administration** | - Fixed scheduled opioid therapy for cancer pain:<br>prior opioid analgesic treatment: oxycodone, morphine, hydromorphone or fentanyl only (oral route and transdermal patch, variable dose according to study's phases)<br>- Rescue therapy for breakthrough cancer pain:<br>oxycodone, morphine, hydromophone, fentanyl or paracetamol (oral route and transdermal patch, flexible dose according to efficacy and safety patient response)<br>- Adjunctive analgesic medication, and Adjuvant therapy for cancer (according to concomitant treatments authorised in the protocol) |
| **Criteria for evaluation: Efficacy and Safety:** | Not applicable |
| **Statistical methods:** | No statistical analysis and description were performed, only listings of individual data were performed. |

**Summary - Conclusions:**

**Patient disposition:**

A total of 14 patients were selected, of whom 8 were randomised and 7 were treated (received and in-taken study drug, 5 in the F13640 group and 2 in the placebo group).

Among the 7 treated patients, 4 patients withdrew prematurely (3 in the F13640 group and 1 in the placebo group) and 3 patients completed the study (2 in the F13640 group and 1 in the placebo group).

**Efficacy results:**

In the descriptive review, the graphs of patients treated less than 7 days could not show any trend, and the graphs of the 3 patients (n°10601, 10801, 50301) treated at least 28 days with F13640 at 2 mg/day showed no relevant evolution.

**Safety results:**

No unexpected event, clinical or biological, were reported in the 7 treated patients, according to the specificity of the study population (cancer patients).

Most AE (such as dizziness, headache, asthenia, nausea, hypotension…) were reported in patients receiving F13640. Related TEAEs were mild or moderate and occurred once (except dizziness which occurred twice in a patient) mainly during up-titration period. Only one patient had TEAE (headache, insomnia, dry mouth then moderate nausea) leading to premature withdrawal with relationship judged not excluded by the Investigator. One SAE (increase of dyspnoea) occurring at D8 in a completer patient with a lung cancer was assessed not related to F13640 by the Investigator.

For 3 patients treated at least 28 days, the tolerability of F13640 allowed increase of doses up to 2 mg/day and maintenance of this target dose until end of treatment period, without occurrence of withdrawal symptoms at the discontinuation of F13640.

**Conclusion**:

Due to the very small size of the population actually studied, no formal conclusion can be drawn about F13640 efficacy in patients suffering from cancer pain (only 3 patients were treated at least 28 days with F13640 at 2 mg/day).

Regarding safety, AE observed were those commonly reported with F13640. Only one patient withdrew due to an adverse event and no SAE were related to F13640 intake. The tolerability of F13640 (in patients treated at least 28 days), allowed increase of doses up to 2 mg/day. No AE occurred during the 10-day post-treatment follow-up period and no signs of individual withdrawal symptoms were detected. AE need to be interpreted in light of the poly-pathology and concomitant symptoms usually observed in this specific population.

**Date of report: May 18, 2010**

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