1 Title page

FINAL INTEGRATED CLINICAL TRIAL REPORT

AN OPEN-LABEL, EXTENDED, FOLLOW-ON STUDY FOR SUBJECTS WITH SEVERE CHRONIC LOW BACK PAIN OR CHRONIC SEVERE PAIN DUE TO OSTEOARTHRITIS OF THE KNEE WHO HAVE COMPLETED ANY OF THE PREVIOUS PHASE IIIB CLINICAL TRIALS OF TAPENTADOL HYDROCHLORIDE KF5503/42, KF5503/43, KF5503/44 OR KF5503/45

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Protocol code: GRT-CG5503-2009-01-ES
Phase of development: IIIb
Status: Final v4.0

Sponsor's responsible:
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2 Synopsis

Sponsor: Grünenthal Pharma, S. A. **Name of the Finished Product:** Palexia **Name of the Active Ingredient:** Tapentadol hydrochloride	**Individual study table referring to part of the dossier:** **Part:** **Vol.:** **Pages:**	**(For National Authority Use only)**

TITLE OF THE STUDY: An open-label, extended, follow-on study for subjects with severe chronic low back pain or chronic severe pain due to osteoarthritis of the knee who have completed any of the previous phase IIIb clinical trials of tapentadol hydrochloride KF5503/42, KF5503/43, KF5503/44 or KF5503/45.

INVESTIGATORS:

Investigators and centres: A total of 17 Spanish investigators participated in the study. A full listing is included in the Appendices.

Studied period: 600 days (patient with the longest follow-up) **First patient included on:** 23 December 2009 **Last patient completed on:** 14 December 2011	**Phase of development:** IIIb

STUDY OBJECTIVES:

Primary objective:

To offer treatment with tapentadol hydrochloride to subjects who have completed the KF5503/42, KF5503/43, KF5503/44 or KF5503/45 clinical trials and may benefit from continued analgesia with tapentadol hydrochloride.

Secondary objectives:

- To evaluate the long-term effectiveness, tolerability and safety of prolonged treatment with tapentadol hydrochloride in subjects with chronic severe low back pain or pain caused by osteoarthritis of the knee coming from protocols KF5503/42, KF5503/44, KF5503/43 and KF5503/45.
- To evaluate the long-term WHO Step I analgesics and/or co-analgesics sparing effect of tapentadol hydrochloride in subjects who previously have reduced or stopped these drugs during Substudy A of the preceding trials.

STUDY DESIGN:

This was a multicenter, open-label, long-term, extension clinical trial carried out in Spain. Patients came from four international phase IIIb clinical trials, hereinafter referred as 'preceding trials'.

The first assessment was done the same day of the Visit 12 of the preceding trial. Participating patients continued to receive the Investigational Medicinal Product (tapentadol hydrochloride PR) at the same dose than in the preceding trial for a period of up to 88 weeks. The study included an initial 4-week transition period, in which the Investigator performed weekly telephone calls to patients and one visit at Week 4. This period was followed by 84 weeks of continued treatment with tapentadol hydrochloride PR with eventual dose modifications. During this period, follow-up visits were performed quarterly. Individual appointments for interim visits were made when the dose of tapentadol hydrochloride PR had to be re-titrated.

The primary purpose of this study was to provide continuous open label treatment to subjects benefiting from tapentadol hydrochloride PR who complete the phase IIIb trials of this drug. In such studies, the analgesic regimen was optimized by up-titrating tapentadol hydrochloride PR and tapering WHO Step 1 analgesics and co-analgesics. In consequence, it was assumed that most patients entering this Extension clinical trial would continue with the dose of tapentadol hydrochloride with which they completed the preceding trial. Nevertheless, under certain circumstances, such doses could be increased during this extension study. The modifications of the doses of concomitant analgesics and co-analgesics were discouraged and the Investigators were instructed to not compromise pain relief or the stability of the tapentadol hydrochloride dose because of the modification of concomitant analgesics. Such recommendations aimed to ensure that only those patients getting continued benefit from tapentadol hydrochloride PR remained in this extension study, which, in turn, would permit testing the secondary objectives of evaluating the long-term effectiveness and tolerability of prolonged treatment with tapentadol hydrochloride PR at a stable dose.

PLANNED TOTAL SAMPLE SIZE:

The primary objective of this study did not entail statistical inferences and, therefore, the statistical power was not defined beforehand. The sample size was determined by the number of eligible patients who completed any of the preceding trials.

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SELECTION CRITERIA:

Key inclusion criteria (see the complete set within this document):

- Subjects who have completed the Continuation Period (Weeks 9 to 12) of the preceding trials KF5503/42, KF5503/43, KF5503/44 or KF5503/45 without any known major protocol violation at the time of completion.
- Patients who met the minimum target of titration during the preceding trial and who continue meeting it at the Baseline Visit of the Extension clinical trial.
- Patients who, in the opinion of the Investigator, would benefit from continued treatment with tapentadol hydrochloride PR for chronic severe low back pain (protocols KF5503/44 and KF5503/45) or chronic severe pain due to osteoarthritis of the knee (protocols KF5503/42 and KF5503/43).
- Signed and dated written informed consent to participate

Key exclusion criteria:

- Known history of, or laboratory values reflecting severe renal impairment or known history of moderately or severely impaired hepatic function.
- History of, or active hepatitis B or C, or history of HIV infection within the past 3 months.
- History of seizure disorder or epilepsy.
- Any of the following within 1 year: mild/moderate traumatic brain injury, stroke, transient ischemic attack, or brain neoplasm. Severe traumatic brain injury within 15 years or residual sequelae suggesting transient changes in consciousness.
- Pregnant or breast-feeding.
- History of allergy to, hypersensitivity to, or contraindications related to tapentadol hydrochloride.
- Use of monoamine oxidase inhibitors.
- Non-stable dosing of selective serotonin reuptake inhibitors.
- Premature discontinuation of tapentadol hydrochloride in the preceding trial for any reason.

CRITERIA FOR EVALUATION:

Effectiveness and quality of life endpoints:

- Average pain intensity score on a 11-point NRS-3 at each visit.
- Patient Global Impression of Change (PGIC) and Clinician's Global Impression of Change (CGIC).
- Sleep Evaluation Questionnaire (SQ) items.
- Subject's satisfaction with treatment.
- EuroQol-5 Dimensions (EQ-5D) scores.
- Short Form 36® Health Survey (SF-36®) scores.
- Requirement for any tapentadol hydrochloride PR dose increase.
- Possibility to reduce the dose of concomitant WHO Step I analgesics or co-analgesics.
- Western Ontario McMaster Questionnaire (WOMAC) scores (patients coming from KF5503/42 and KF5503/43 studies.
- Average pain intensity score on a 11-point NRS-3 for pain radiating towards or into the leg (for patients from the KF5503/44 and KF5503/45 studies with neuropathic pain component).
- SF-MPQ (idem).
- NPSI (idem).

Safety and tolerability endpoints:

- Cumulative incidence of adverse events and adverse drug reactions during the Extension clinical trial.
- Association of adverse events to concomitant analgesic treatment and their relationship to tapentadol hydrochloride PR as judged by the Investigator.
- Vital signs.
- Clinical laboratory values.

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STATISTICAL ANALYSES:

All the data was analysed descriptively. Continuous variables were described with the mean, standard deviation, median, first and third quartiles and the range. Categorical variables were described as numbers and frequencies. These analyses were done over the data available. Missing values because of premature withdrawal or any other reason were not imputed.

Separate descriptive analyses were done for each visit of the Extension clinical trial. The Cumulative incidence of adverse events and adverse drug reactions were calculated for the total duration of the Extension clinical trial. Also, incidence rates were calculated to account for the differences in the duration of the Extension clinical trial from subject to subject and given as cases per subject and time unit.

RESULTS:

A total of 83 patients, from 132 participating in the preceding studies (63%), were enrolled in the Extension clinical trial. Twenty-one patients withdrew prematurely. Adverse events was the most common reason (7 patients). Approximately one half of patients had knee OA and the other half LBP. Premature withdrawals were evenly distributed between these two groups. Almost three-fourths of patients with LBP featured a neuropathic component. Compliance with the investigational product was very good; on average, tapentadol hydrochloride PR was taken 94% of the days under treatment.

At baseline, pain intensity was mild on average, the health-related quality of life was impaired compared to the normative data of the Spanish population, and the global impression of change was between 'minimally improved' to 'much improved' with respect to the baseline visit of the preceding study.

During the study, the pain intensity did not vary, and most patients did not change their satisfaction ratings. There were slight but significant improvements in the score of the physical functioning scale for patients with knee OA and of the social functioning scale of the SF-36 health survey for patients with LBP. The score of the SF-MPQ improved slightly but significantly in patients with LBP with a neuropathic pain component. Only 7 patients (8%) required a re-titration of tapentadol hydrochloride PR dose during the extension trial.

Patients were exposed to the investigational product at an average dose of 300 mg/day for a median of 505 days. Adverse events were relatively uncommon, with just 55% of patients experiencing at least one. However, 67% of the patients with adverse events experienced more than one. The adjusted incidence rate of adverse events was of 0.9 events per patient per year. Eighteen percent of patients experienced at least one adverse event related to the investigational products (adverse drug reaction). The system organ class most frequently involved by adverse event was infections and infestations. The system organ class most frequently involved in adverse events related to the investigational product was the gastrointestinal. Constipation was the single adverse event most frequently reported (8% of patients). Seven percent of patients experienced a serious adverse event; none was considered to be related to the investigational products. The adverse events that led to premature withdrawal (8% of patients) involved typically the gastrointestinal system.

DISCUSSION:

Compared with extension studies performed with other opioids, tapentadol has shown a favourable tolerability profile, with less patients experiencing adverse events and withdrawing prematurely in this study.

Also the proportion of patients experiencing adverse events in this extension study was lower than in prior Phase III clinical trials with tapentadol, including the studies active controlled with oxycodone and the studies preceding this extension trial. This difference may be explained by the fact that opioid-related side effects usually concentrate during the first weeks of treatment, and patients in this study had been treated for 12 weeks before entering it. [redacted]

In conclusion, oral tapentadol prolonged release was considerably safe and provided a sustained, effective analgesic effect against chronic noncancer pain with or without neuropathic features in most of the patients who were selected to participate in the preceding Phase IIIb clinical trials without the need for dose re-titrations.

Date of the report: June 2013