Trial number	KF5503/42
Title of trial	An evaluation of the effectiveness and tolerability of tapentadol hydrochloride prolonged release, and tapentadol hydrochloride immediate release on demand, in subjects with uncontrolled severe chronic pain due to osteoarthritis of the knee taking either WHO Step I or Step II analgesics or no regular analgesics.
EudraCT number	2009-010423-58
Publication number	441172
Development phase	Phase IIIb
Investigational medicinal products	Tapentadol hydrochloride prolonged release (PR) and tapentadol hydrochloride immediate release (IR)
Indication	Chronic pain due to osteoarthritis of the knee
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany Phone: +49 (0) 241 569 0, Fax: +49 (0) 241 569 2623
Coordinating investigator	[redacted] [redacted] Cantabria 39300, Spain Phone: [redacted]
Trial period	First subject enrolled: 21 Sep 2009 Last subject completed: 02 Sep 2010
Trial design	Multicenter, multinational, open-label, effectiveness Phase IIIb trial.
Trial centers	In total, 23 active centers: 4 in France, 7 in Germany, 2 in Poland, 5 in Spain, and 5 in the United Kingdom.

Objectives:

The primary objective was to evaluate the effectiveness, tolerability, and safety of tapentadol hydrochloride PR in subjects with chronic pain due to osteoarthritis of the knee taking either WHO Step I or Step II analgesics or no regular analgesics and showing lack of efficacy.

Secondary objectives in the population under study were to:

- Demonstrate that tapentadol hydrochloride PR produces a better analgesia than previous Step I and Step II analgesics.
- Evaluate the conversion of subjects from previous WHO Step II analgesics to tapentadol hydrochloride PR.
- Evaluate the titration of tapentadol hydrochloride PR in clinical practice.
- Evaluate whether the treatment with tapentadol hydrochloride PR can produce a reduction in the need for WHO Step I analgesics and co-analgesics (sparing effect).
- Evaluate whether the treatment with tapentadol hydrochloride PR can produce a reduction in the need for medications (anti-emetics and laxatives) to treat opioid-related adverse events in subjects previously treated with WHO Step II opioid analgesics.

- Evaluate the impact of tapentadol hydrochloride PR on function and quality of life parameters (subject-reported outcomes) in subjects with pain due to osteoarthritis of the knee.

Investigational medicinal products:

Tapentadol hydrochloride PR

Substance code:	CG5503.		
Substance name:	Tapentadol hydrochloride.		
Batch numbers:	Dose	Batch	Expiry date
	50 mg	103M06	04/2011
	50 mg	103M08	04/2011
	100 mg	101M08	04/2011
	150 mg	103M07	04/2011
	150 mg	101M11	03/2011
	200 mg	101L15	10/2010
	200 mg	102A06	06/2012
	250 mg	101L16	09/2010
	250 mg	102L05	09/2010
	50 mg	103M06	04/2011
Composition:	Each PR tablet contains tapentadol hydrochloride 58 mg, 116 mg, 175 mg, 233 mg, and 291 mg corresponding to 50 mg, 100 mg, 150 mg, 200 mg and 250 mg tapentadol free base.		
Administration:	Oral, twice daily.		

Tapentadol hydrochloride IR

Substance code:	CG5503.		
Substance name:	Tapentadol hydrochloride.		
Batch numbers:	Dose	Batch	Expiry date
	50 mg	104M06	01/2011
Composition:	Each IR tablet contains 58 mg tapentadol hydrochloride corresponding to 50 mg tapentadol free base.		
Administration:	Oral, on demand, up to 2 tablets per day at least 4 hours apart.		

Treatments:

Tapentadol hydrochloride PR

If eligible, all the subjects started the treatment with tapentadol hydrochloride PR (50 mg twice daily), the morning after completing the Baseline Visit. The previous WHO Step II analgesic regimen was continued until the evening of the day of the Baseline Visit. The dose of tapentadol hydrochloride PR was titrated weekly (upwards or downwards), with a maximum dose of 250 mg

twice daily (500 mg total daily dose), depending on pain levels and tolerability. An interim titration could also take place 3 days (evening of Day 3 or morning of Day 4) after starting the treatment with tapentadol hydrochloride PR. The subject was required to visit the site for all dose adjustments. After Week 5, the doses of tapentadol hydrochloride PR were kept stable.

Tapentadol hydrochloride IR

Tapentadol hydrochloride IR 50 mg (no more than twice daily; at least 4 hours apart) was considered as a backup medication to be used where other medication did not provide adequate relief of acute pain. It was given for:

- Acute pain due to the index pain:
  - Without a clear cause.
  - Due to increased activity or movement (incidental pain).
  - End-of-dose failure indicating a requirement for adjustment of the dose of tapentadol hydrochloride PR.
- Withdrawal symptoms such as hyperalgesia that could have appeared during the first days of titration after the previous treatment with an opioid had been stopped.

Tapentadol hydrochloride IR was not to be given to subjects who were taking tapentadol hydrochloride PR 250 mg twice daily (500 mg total daily dose).

Trial population:

The trial included men or non-pregnant, non-lactating women of at least 40 years of age with a diagnosis of osteoarthritis of the knee requiring a strong analgesic (WHO Step III) and a rate of satisfaction with their previous analgesic regimen not exceeding “fair” on a subject satisfaction with treatment scale. If under regular, daily pre-treatment with a WHO Step I or Step II analgesic, subjects had to have an average pain intensity score (NRS-3) greater than 5 points during the last 3 days prior to the Screening Visit and the investigator considered dose increase of WHO Step I analgesics (as mono- or combination therapy) and/or continuation with or dose increase of WHO Step II analgesics inadequate. If no regular analgesic treatment was reported, subjects had to have pain related to the osteoarthritis of the knee with an average NRS-3 score greater than 6 points in the last 3 days prior to the Screening Visit.

Methodology:

Multicenter, multinational, open-label, effectiveness Phase IIIb trial.

This trial included 2 substudies. In Substudy A, subjects tapered their concomitant WHO Step I analgesics or co-analgesics to determine the sparing effect under treatment with tapentadol hydrochloride PR. In Substudy B, they reduced their use of concomitant medication related to opioid-induced adverse events of previous Step II analgesics.

The trial lasted up to 13 weeks for each subject and included:

I. Observation Period: Week -1

During Week-1, the investigator documented different efficacy and quality of life parameters related to the analgesic regimen of the subjects prior to the start of the IMP, including adverse events, particularly those that he or she judged as associated with the analgesics/co-analgesics.

Subjects were screened to assess their eligibility at the Screening Visit, and enrolled if the inclusion criteria for entering the Observation Period were fulfilled and no exclusion criteria met. Blood samples were collected for laboratory analysis. Quality of life questionnaires (EuroQol-5 dimension [EQ-5D] and short form 36® health survey [SF36], sleep evaluation questionnaire [SQ], and hospital anxiety and depression scale [HADS]) were completed. The history of the osteoarthritis-related knee pain was explored by additional questions including those related to the treatments received prior to the current analgesic regimen, number of regimen switches or treatment discontinuations, and functionality. Adverse events associated with analgesics and co-analgesics, if applicable, were recorded.

During Week -1, the subjects documented the use of analgesics and concomitant medication (co-analgesics and medication related to treatment of opioid-induced side effects) in the eDiary. The daily doses of analgesics used during the last 3 days prior to the Baseline Visit were recorded into the electronic Case Report Form.

At the Screening Visit and the Baseline Visit, the subject's pain intensity score (using an 11-point NRS-3) and adverse events were recorded.

If applicable, WHO Step II analgesics were stopped at the end of Week -1, before the start of the IMP.

II. Titration and stabilization Period: Week 1 to Week 5

Subjects started their treatment with tapentadol hydrochloride PR on the morning following the Baseline Visit.

An interim telephone contact took place 3 days after starting the treatment with tapentadol hydrochloride PR to check if a dose adjustment was necessary.

Subjects went to the site at Visit 1 (after 1 week of treatment) and Visit 5 (after 5 weeks of treatment), and were contacted by telephone for Visit 2, Visit 3, and Visit 4 (after 2, 3, and 4 weeks of treatment). At the visits, adverse events, concomitant medication taken and key parameters of functionality and quality of life were recorded.

The subject had to visit the site for all dose adjustments, including potential additional visits for dose reduction in case of lack of tolerability.

Doses of WHO Step I analgesics and co-analgesics, as well as medication related to opioid-induced side effects of the previous opioid regimen were kept stable during this period.

III. Optimal dose Period: Week 6 to Week 8

Subjects continued their treatment with tapentadol hydrochloride PR at the stabilized dose.

Week 6 was the week of comparison to Week -1 for the primary endpoint.

At Visit 6, suitable subjects (in the investigator's opinion) who consented were assigned to Substudy B. The medication given to alleviate adverse reactions of previous opioid therapy (i.e., anti-emetics and laxatives) was tapered and stopped during Week 7. The subjects were suitable if they had reported no or only mild nausea, vomiting or constipation at Visit 6. Tapering could be done in 2 steps (halving the dose after Visit 6, and stopping the adverse event-related medication at

Day 3 or the morning of Day 4 of Week 7). If nausea, vomiting or constipation returned or worsened, the investigator could stop tapering.

IV. Continuation Period: Week 9 to Week 12

Subjects continued their treatment with tapentadol hydrochloride PR at the stabilized dose. Tapentadol hydrochloride IR could be taken within the predefined regimen for incidental pain as needed (not exceeding a total daily dose of 500 mg tapentadol PR plus IR inclusive).

For subjects who consented, WHO Step I analgesics or co-analgesics were tapered without compromising the pain relief obtained with tapentadol hydrochloride PR and without adjustment of the tapentadol hydrochloride PR and average tapentadol hydrochloride IR dose to determine the sparing effect (Substudy A).

Data collected:

Primary endpoint

The primary endpoint was defined as the change from Week -1 of the average pain intensity score on the 11-point numeric rating scale during the last 72 hours (NRS-3) at Week 6.

Efficacy and quality of life endpoints

- Time to clinically relevant pain relief.
- Time to effectiveness.
- Number of dose adjustments needed to reach the minimum target of titration (at least the same pain intensity score on the 11-point NRS-3 compared to baseline).
- Reduction of concomitant Step I analgesics and co-analgesics (Substudy A).
- Reduction in use of concomitant medication related to opioid-induced adverse events of previous Step II analgesics (Substudy B).

Comparisons were made between Week -1 and Week 6, Week 8, and Week 12 for:

- Responder rate 1 (percentage of subjects with a decrease of at least 1 point in the pain intensity score on the 11-point NRS-3).
- Responder rate 2 (percentage of subjects with a decrease of at least 1 point in the pain intensity score on the 11-point NRS-3 and an improvement of at least 1 category on the subject's satisfaction with treatment [5-point VRS] from Week -1 to Week 6).
- Western Ontario McMaster questionnaire scores.
- Patient's global impression of change.
- Clinician's global impression of change.
- Sleep questionnaire items.
- Short form 36® health survey scores.
- Subject's satisfaction with treatment.
- EuroQol-5 dimension scores.
- Hospital anxiety and depression scale.
- Mean daily dose per compound of previous Step I analgesics (comparison of Week 6 with Week -1).

- Mean daily dose per compound of co-analgesics (comparison of Week -1 with Week 6, 8, and 12).

Clinical effectiveness comprised elements of efficacy and general subject satisfaction, and was measured by responder rate 2, accordingly.

Safety and tolerability endpoints

- Adverse events and adverse drug reactions.
- The association of adverse events to previous, concomitant analgesic treatment and their relationship to the investigational medicinal products as judged by the investigator.
- Cumulative adverse events (all adverse events throughout the trial cumulated separately during Week-1 prior to start of investigational medicinal products and separately after start of investigational medicinal products).
- Comparisons of the adverse events that were present (ongoing and newly occurring) were made between Week -1 and Week 6, Week 8, and Week 12 (if Week -1 was shortened to 3 days, the last 3 days of Week 6, Week 8, and Week 12 were used as the basis for the comparison).
- Vital signs.
- Clinical laboratory values.
- Medication used to treat the adverse events produced by previous analgesic treatment and tapentadol hydrochloride.

Statistical methods:

The primary analysis was performed on the Main Analysis Population which consisted of all subjects who received at least 1 dose of tapentadol hydrochloride PR and had at least 1 post-baseline pain intensity assessment.

The primary null hypothesis tested for the trial was that the average pain intensity score was not different at Week 6 compared with Week -1.

The primary efficacy variable was analyzed using a 2-sided t-test. Treatment effects, 95% confidence intervals and p-values were presented for the NRS pain intensity scores at Week 6 compared with Week -1. Missing data for pain intensity scores were replaced with results for the last observation (LOCF imputation) for early terminators of the trial, i.e., subjects who dropped out before Visit 6.

Descriptive comparison of all secondary endpoints was performed for the defined stable treatment weeks (Week 6 to Week 12).

For comparison between stable weeks (e.g., between Week -1 and Week 6), adverse events newly occurring during the respective weeks or ongoing from the previous period (prevalence) were summarized for the respective period (no overall accumulation) in order to allow for realistic comparison under stable conditions.

Any adverse events occurring and ending in the periods between the stable weeks were documented (overall adverse events), but not included in the comparison of outcomes for the stable weeks.

An interim analysis was performed after 113 subjects had completed the trial.

Sample size determination

A standard deviation of 3 for a change in pain intensity score was assumed from earlier trials with tapentadol hydrochloride PR. A difference of 1 between the pain intensity score at Week -1 and the pain intensity score at Week 6 was considered clinically relevant in the proposed setting. For a sample size of 73, a single-group 2-sided t-test with a 0.05 significance level would have 80% power to detect the difference between a null hypothesis mean of 5 and an alternative mean of 4, assuming a standard deviation of 3.

For responder rate 1 and responder rate 2, a value of 60% was assumed to be clinically relevant. A 1-group χ^2 test with a 0.05 one-sided significance level would have 85% power to detect the difference between the null hypothesis proportion of 50% and the alternative proportion of 60% for a sample size of 177.

A sample size of 177 was required to perform all tests stepwise, given the rejection of the null hypothesis at the first 2 steps.

The planned sample size was slightly increased to account for the interim analysis of the data. A total of 180 subjects were to be entered to cover this additional analysis.

The targeted minimum number of subjects that allowed for a clinically relevant assessment of the substudies was approximately 30 for Substudy B and approximately 80 for Substudy A.

Summary of results:

Subject disposition

Overall, 224 subjects were enrolled into the trial, 200 subjects (89.3%) were exposed to tapentadol hydrochloride PR and were included in the Safety Set.

Between baseline and Visit 12, 56 subjects (28.0%) discontinued their IMP intake, thereof 24 subjects (12.0%) due to adverse events. Overall, 160 subjects (80.0%) completed Visit 6, and 144 (72.0%) completed Visit 12 as per protocol.

The Main Analysis Population comprised 195 subjects (87.1%) and the Per Protocol Set 124 subjects (55.4%). A total of 21 subjects (9.4%) were allocated to Substudy A and 1 subject (0.4%) to Substudy B.

	Total
Number of subjects planned to be treated	180
Number of subjects enrolled	224
Number of premature terminations during the Observation Period	24
	n (%)
Number of subjects receiving trial medication	200 (100.0)
Number of premature terminations between Baseline and Visit 6 (excluding Visit 6)	40 (20.0)
Number of premature terminations between Visit 6 and Visit 12	16 (8.0)
Number of premature terminations between Baseline and Visit 12	56 (28.0)
Reasons for premature terminations:	
Safety reasons not related to the IMP	0 (0.0)
Adverse events	24 (12.0)
Pregnancy	0 (0.0)
Withdrawal of consent for any reason	13 (6.5)
Lost to follow up	0 (0.0)
Lack of efficacy	7 (3.5)
Non-compliance	1 (0.5)
Death	0 (0.0)
Other	11 (5.5)

n = Number of subjects with data available, % = Percentage based on number of subjects receiving investigational medicinal product.

Demographics

A total of 200 subjects (135 women and 65 men) were included in the clinical trial in the Safety Set; most subjects were white. Subjects presented with a mean age of 67.4 years and a mean body mass index of 31.88 kg/m^2.

History of osteoarthritis-related knee pain

The mean duration of osteoarthritis-related knee pain for all subjects in the Safety Set was 8.29 years with a wide range of 0.1 years to 43.2 years; the mean time to the first visit/consultation of a physician because of this pain was 8.61 months (range 0.0 months to 240.0 months). On average subjects had visited 2.72 physicians (maximum 8) since their pain started, consulted their physician for a mean number of 2.22 visits in the last 3 months (maximum 10), and had 0.71 (maximum 6) unplanned consultations within the last 3 months. Twenty-five subjects (12.5%) were hospitalized up to 4 times due to their osteoarthritis-related knee pain. Subjects had taken up to 20 different analgesics regimens since their pain started (average 3.37). The main reason for a change in the regimen for the previous treatments was a lack of efficacy. Adverse events were less frequently reported as a reason to change the analgesic regimen.

Prior medication

Only 44 of 200 subjects (22.0%) reported the prior use of analgesics or co-analgesics at the Screening Visit that was stopped before subjects were enrolled into the trial. The WHO Step I analgesics were used by 18.5% of the subjects (mostly diclofenac [sodium], ibuprofen, or rofexocib), WHO Step II analgesics such as opioids (tramadol, tramadol hydrochloride, or the

fixed-dose combination products tramadol/paracetamol, codeine phosphate/paracetamol, or naloxone/tilidine hydrochloride) by 6.0% of the subjects, and WHO Step III analgesics buprenorphine or the fixed-dose combination product naloxone hydrochloride/oxycodone hydrochloride by 1.5% of the subjects. Co-analgesics were used by 2.5% of the subjects and comprised doxepin, a herbal preparation, lidocaine, pregabalin, tetrazepam, or topical products for joint and muscular pain. Eleven subjects (5.5%) took a non-analgesic medication not related to opioid-induced side effects (of previous opioid regimen).

Medication intake during Week -1

During Week -1, 185 subjects (92.5%) reported the use of analgesics or co-analgesics in their eDiary. The WHO Step I analgesics were reported by 160 subjects (80.0%). The most frequently reported were diclofenac (sodium) followed by paracetamol, ibuprofen, celexocib, or metamizole containing products. Fifty-eight subjects (29.0%) took WHO Step II analgesics, thereof 15 subjects codeine phosphate/paracetamol, 17 subjects tramadol (or tramadol hydrochloride), and 11 subjects paracetamol/tramadol hydrochloride. Step III analgesics (morphine, oxycodone hydrochloride, or naloxone hydrochloride/oxycodone hydrochloride) were documented for 2 subjects and co-analgesics for 32 subjects (16.0%) (most frequently pregabalin and capsaicin).

Most subjects (89.0%) used non-analgesic medication not related to opioid-induced side effects of previous opioid regimens, e.g., agents acting on the renin-angiotensin system (in 53.0% of the subjects), beta blocking agents (29.0%), lipid-modifying agents (28.5%), or drugs used in diabetes (25.5%).

Concomitant medication

Overall, 136 of 200 subjects (68.0%) used concomitant analgesics or co-analgesics during the trial; WHO Step I analgesics were used concomitantly with the IMP by 129 subjects (64.5%). Most frequently used were paracetamol, diclofenac (sodium), ibuprofen, and etorixocib. The concomitant use of a WHO Step II analgesic was reported for 3 subjects (1.5%) (paracetamol/codeine phosphate, tramadol, or a combination product containing ascorbic acid, codeine phosphate, diprophylline, metamizole sodium, and paracetamol). For 2 subjects (1.0%), the use of the WHO Step III analgesics (buprenorphine or morphine) was reported. Co-analgesics were used by 34 subjects (17.0%). The pattern of use for co-analgesics was similar to Week -1.

The pattern of concomitant non-analgesic medication not related to opioid-induced side effects (of previous opioid regimen) was similar to Week -1 as well. Overall, 90.5% of subjects needed concomitant non-analgesic medication during the trial, mainly agents acting on the renin-angiotensin system (53.5%), beta blocking agents (29.5%), lipid modifying agents (29.0%), drugs for acid related disorders (26.0%), drugs used in diabetes (25.5%), anti-thrombotic agents (24.0%), diuretics (20.5%), %), calcium channel blockers (18.0%), psycholeptics (15.0%), and thyroid therapy (12.0%).

Medication for opioid-induced side effects of previous treatments

During Week -1, 9 subjects (4.5%) took laxatives or other medication to treat side effects. During treatment with tapentadol hydrochloride, 30 subjects (15.0%) reported the intake of side effect medication. This includes drugs taken during Week -1 which were continued according to protocol. Most frequently reported were laxatives and others.

Association of adverse events with previous analgesic/co-analgesic medication

For 10 subjects (5.0%) of the Safety Set, non-treatment emergent adverse events (non-TEAEs) were considered by the investigator to be at least possibly associated to the intake of WHO Step I (ibuprofen or naproxen), Step II (tramadol, others, or combination products paracetamol/codeine phosphate, paracetamol/tramadol [hydrochloride]), or Step III analgesics (naloxone hydrochloride/oxycodone hydrochloride). In 2 subjects, TEAEs were assessed as at least possibly associated to the Step I analgesic diclofenac or to the Step II analgesic codeine phosphate/paracetamol.

Effectiveness and quality of life parameters

Tapentadol hydrochloride PR was effective in subjects with severe chronic osteoarthritis who had no previous regular analgesic treatment or were regularly pre-treated with non-steroidal anti-inflammatory drugs and/or WHO Step II analgesics with a lack of efficacy.

Primary endpoint, pain intensity, and related parameters

Subjects in the Main Analysis Population (N = 195) presented with a baseline mean (SD) average pain intensity score for Week -1 of 7.5 (1.08) (on the 11-point NRS-3). The mean (SD) change from baseline to Week 6 (using LOCF for imputing missing scores, N = 193 evaluable subjects) was -3.4 (2.10) and was statistically significant ($p < 0.0001$). Changes in the average pain intensity were similar in subjects being opioid naïve (-3.4 [2.07], N = 139) or pre-treated with opioids (-3.4 [2.18], N = 54) and statistically significant ($p < 0.0001$) in both subgroups.

A total of 155 of 160 subjects (96.9%) were classified as responders (responder rate 1) at Visit 6 in the Main Analysis Population (without LOCF imputation of missing values for this dataset). There was no difference between subjects pre-treated with opioids and opioid-naïve subjects. When LOCF imputation was applied for missing data, a total of 179 of 195 subjects (91.8%) were classified as responders at Visit 6 and 14 subjects (7.2%) as non-responders. The responder rate 1 increased over time from the Interim Visit to Visit 12 and was similar when subjects who tapered their concomitant WHO Step I analgesics and co-analgesics in the Continuation Period were included into the analyses.

At Visit 6, 142 of 160 subjects (88.8%) achieved a decrease of at least 1 point in the pain intensity score on the 11-point NRS-3 from Week -1 to Week 6 and an improvement of at least 1 category on the subject's satisfaction with treatment (5-point VRS) (responder rate 2, without LOCF imputation of missing values for this dataset).

The mean pain intensity scores (11-point NRS-3) decreased over time from baseline (7.5) to Visit 8 and remained at a low level up to Visit 12. Once an optimal dose of tapentadol hydrochloride PR was reached, mean NRS-3 values remained around 3. At Visit 6, the mean changes from baseline for all subjects in the Main Analysis Population were -3.8, at Visit 8 it was -4.2, and at Visit 12 -4.4 (without LOCF imputation). Subjects pre-treated with opioids presented with a similar mean baseline score (7.6) and a change from baseline at Visit 12 (-4.6) compared to opioid-naïve subjects (with baseline pain scores of 7.5 and changes from baseline at Visit 12 of -4.3). Also, the LOCF analysis (for Visit 6, Visit 8, and Visit 12) or the inclusion of subjects who participated in Substudy A at Visits 9-12 showed similar results.

The WOMAC Osteoarthritis Index was chosen as a complementary assessment of effectiveness. All scores for the dimensions pain, stiffness, and physical function, and for the global score were reduced during the course of the trial. Changes to baseline were statistically significant at the time points that were evaluated.

Tapentadol dosing in relevant subsets

Most responders (responder rate 1) achieved a decrease of at least 1 point in the pain intensity score on the 11-point NRS for the first time up to Visit 6 with their initial tapentadol hydrochloride PR dose (140 of 195 subjects, 71.8%) or with only 1 adjustment (25 subjects, 12.8%).

The mean (SD) final stable dose of tapentadol hydrochloride PR at Visit 6 for all subjects was 256.9 (111.38) mg/day (median 200 mg/day, range 100 mg/day to 500 mg/day). Few subjects only (6.9%) took tapentadol hydrochloride at a dose of 2 x 250 mg per day to achieve an acceptable and stable reduction of their chronic pain due to osteoarthritis of the knee. In opioid-naïve subjects, the final stable dose on average was 253.4 (113.01) mg per day (n = 116) with a median of 200 mg and a range of 100 mg to 500 mg. In subjects pre-treated with opioids, the final stable dose was 265.9 (107.71) mg per day (n = 56) with a higher median of 300 mg.

Most subjects (142 of 160 [88.8%]) did not need to be treated with additional tapentadol hydrochloride IR at Visit 6 and 3.1% (5 of 160) took 2 x 50 mg. The mean daily dose of tapentadol hydrochloride IR at Visit 6 for all subjects was 6.7 mg, in subjects pre-treated with opioids 12.9 mg, and in opioid-naïve subjects 4.3 mg.

Quality of life functions and related parameters

With respect to the quality of life analysis performed in this trial, tapentadol hydrochloride PR demonstrated a considerable improvement in the quality of sleep, the SF-36 health survey scores, and the EQ-5D. Data were similar when missing data were imputed or when subjects participating in Substudy A were included in the analyses.

At baseline, 47.2% of the subjects classified their overall quality of sleep as “fair”, 40.0% as “good”, 9.2% as “poor”, and 2.6% as “excellent”. At Visit 6, 38.8% of the subjects rated their overall quality of sleep as improved compared with baseline, 52.5% as no change and 6.9% as worsening. Similar results were reported at Visit 8 (44.5%, 47.1% and 6.5%) and Visit 12 (40.0%, 50.4% and 8.8%).

The mean changes from baseline for the EQ-5D index scores were 0.2302 at Visit 6, 0.2415 at Visit 8, and 0.2726 at Visit 12. All improvements were statistically significant. The mean scores for patient’s health assessment increased by 15.8 at Visit 6, 17.6 at Visit 8, and 19.5 at Visit 12; again these changes were statistically significant.

For all health domain scales of the Short form 36 health survey, there were statistically significant changes in the mean scores from baseline to Visit 6, Visit 8, or Visit 12 indicating an increase in subjects’ general health status.

Subjects were satisfied with the new treatment they received. The analysis of changes from baseline showed 90.0% of improvement at Visit 6, 92.3% at Visit 8, and 90.4% at Visit 12.

Clinician’s and patient’s global impression of the change introduced by the new treatment was generally very good. For the PGIC, most of the subjects reported that their overall condition had

"not changed" (32.8%) or had "minimally improved" (50.5%) at the Interim Visit. At Visit 12, 18.4% of the subjects reported that their condition had "very much improved", 51.2% reported "much improved", 26.4% "minimally improved", and 4% "no change".

Most of the clinicians evaluated the overall condition of their subjects (CGIC) accordingly at Visit 12 with "very much improved" for 22.4% of their subjects, "much improved" for 54.4% of the subjects, "minimally improved" for 21.6%, and "no change" for 1.6%.

Parameters related to anxiety and depression

Subjects enrolled in this trial had no clinically relevant anxiety or depression at baseline. All the values on the HADS scales were below or just at the threshold of 7

Effectiveness and quality of life in the Substudy A Set

Twenty-one subjects consented to and participated in Substudy A and tapered their concomitant WHO Step I analgesics and co-analgesics between Week 9 and Week 11. Two subjects dropped out between Visit 8 and Visit 12 for technical reasons.

Twenty of 21 subjects (95.2%) planned to reduce their Step I analgesics. Diclofenac, diclofenac/misoprostol, etorixocib, ibuprofen, indometacin, metamizole sodium, naproxen, and paracetamol were tapered completely by 16 of 20 subjects and to 50% by 2 subjects; 2 subjects did not succeed tapering their paracetamol intake. One further subject (4.8%) tapered completely the co-analgesic duloxetine hydrochloride. The reduction in the dose of concomitant Step I analgesics and co-analgesics did not compromise the pain reduction achieved with tapentadol hydrochloride.

The mean pain intensity scores (11-point NRS-3) decreased over time from baseline (8.0) to Visit 6 (4.2). At Visit 8, they were reduced to 4.0 and were further reduced during the tapering period until Visit 12 (3.7). At Visit 6, Visit 8, and Visit 12, the changes from baseline were statistically significant ($p < 0.0001$).

All scores of the WOMAC domains were reduced during the course of the trial. Changes to baseline were statistically significant at Visit 6, Visit 8, and Visit 12. However, the scores of the individual domains did not change considerably after the subjects had reached a stable tapentadol hydrochloride dose at Visit 6.

The responder rate 1 was 100% at Visit 6 and remained high at 85.7% to 100% for Visit 9 to Visit 12. The responder rate 2 was 95.2% at Visit 6 and ranged from 85.7% to 95.2% for Visit 9 to Visit 12. The maintenance of the high responder rate 1 and responder rate 2 at Visit 12 confirms as well that the tapering of WHO Step I analgesics and co-analgesics did not impair the analgesia achieved with tapentadol hydrochloride.

The mean (SD) final stable dose of tapentadol hydrochloride PR at Visit 6 for the Substudy A set was 214.3 (85.36) mg per day and was lower than for all subjects participating the trial.

Results of the quality of life and effectiveness endpoints were not different from those of the overall trial population.

Safety and tolerability:

The TEAEs that affected at least 5% of the subjects were constipation (in 10.5% of subjects), diarrhea (5.5%), dry mouth (10.0%), nausea (13.0%), vomiting (5.0%), fatigue (10.5%),

nasopharyngitis (8%), dizziness (12.0%), headache (6.5%), and somnolence (7.0%). All but nasopharyngitis were known adverse drug reactions of tapentadol hydrochloride. Twenty-five subjects (12.5%) had TEAEs that led to their premature termination of the trial, 20 of whom had TEAEs related to the IMP and 1 had an associated event (diarrhea). Treatment discontinuations due to TEAEs were lower than in Phase III trials in the same indication.

Overall, 8 subjects (4%) reported 10 serious TEAEs, only 1 of them (panic attack) was considered probably/likely related to the IMP.

Neither deaths nor pregnancies were reported in this trial.

No clinically relevant changes were observed in vital parameters, laboratory values or physical examination parameters.

No new adverse drug reactions of tapentadol hydrochloride were identified.

The AE profile observed in this trial was similar but with lower frequencies of TEAEs than in the previous Phase III trial in OA with similar treatment duration, confirming the stable AE profile of tapentadol.

The co-administration of tapentadol hydrochloride IR on top of tapentadol hydrochloride PR did not alter the tolerability.

Overall, the favorable safety and tolerability profile of tapentadol was confirmed in this Phase IIIb trial.

Conclusion:

The results of this trial have to be interpreted in line with the limitations of an open-label trial design.

Tapentadol hydrochloride PR was effective in the treatment of severe pain from OA of the knee in subjects whose previous WHO Step I or Step II analgesic regimens showed lack of efficacy.

The effectiveness of tapentadol hydrochloride PR was shown in opioid-naïve and opioid-pretreated subjects. The evidence of the effectiveness tapentadol hydrochloride PR was proven by a positive result of the primary endpoint (change from Week -1 of the average pain intensity score at Week 6) and of the analysis of the secondary endpoints. Improvements were achieved in pain intensity scores, responder rates, WOMAC Osteoarthritis Index, and other quality of life and function parameters, requiring low average daily doses of tapentadol hydrochloride PR.

Overall, the results of Substudy A indicate that tapentadol–because of its 2 mechanisms of action–can lead to a clinically relevant sparing of analgesics and co-analgesics without impairing analgesia.

Tapentadol hydrochloride PR and IR were administered in this trial for the treatment of OA-related knee pain and the adverse event profile was similar but with lower frequencies of TEAEs than that observed in Phase III trials with tapentadol hydrochloride PR in the same indication and similar treatment duration, but the frequencies of TEAEs and premature terminations were lower than in previous trials with tapentadol hydrochloride IR and PR.

ICTR SYNOPSIS SUPPLEMENT

KF5503/42

Original ICTR issue date:	20 Aug 2013	**DMS version:**	2.0
ICTR synopsis supplement date:	13 Jul 2015	**DMS version:**	1.0

1 SUPPLEMENT CONTENT

This document contains information about the trial that is not already covered in the synopsis of the corresponding clinical trial report.

2 INFORMATION ABOUT PROTOCOL AMENDMENTS

There was 1 amendment to the protocol. The following changes were documented:

- Correction of the wording for the duration of morning stiffness in inclusion criterion 5 that had been mistakenly stated in the original protocol and corrected in a later note to file.
- The signatories of the protocol were reduced to match current Grünenthal standards.
- Clarification was provided on deviations from established visit windows in exceptional cases.
- The English version for the USA of the Western Ontario McMaster Questionnaire was replaced by the version for United Kingdom (UK), resulting in a modification of the wording.
- The scales in the Hospital Anxiety and Depression Scale (HADS) questionnaire were corrected according to the original version for the UK.
- Furthermore, this amendment served to improve the clarity and the consistency within the relevant protocol sections.

This amendment was considered substantial and submitted for approval by the competent authorities and ethics committees in Europe.

3 INFORMATION REGARDING CLINICAL HOLD OR EARLY TERMINATION

This clinical trial was not subjected to a clinical hold or early termination.

4 NAMES AND ADDRESSES OF PRINCIPAL INVESTIGATORS

The names of principal investigators for all sites are not included in the list below because consent for public disclosure was not obtained.

Site number	Investigator	Site address
DE001	(Name not given, since no consent given)	45768 Marl, Germany
DE002	(Name not given, since no consent given)	51069 Köln Dünnwald, Germany
DE003	(Name not given, since no consent given)	38527 Meine, Germany
DE004	(Name not given, since no consent given)	04103 Leipzig, Germany
DE005	(Name not given, since no consent given)	10409 Berlin, Germany
DE006	(Name not given, since no consent given)	04229 Leipzig, Germany

Site number	Investigator	Site address
DE008	(Name not given, since no consent given)	07407 Rudolstadt, Germany
ES001	(Name not given, since no consent given)	Torrelavega, Cantabria 39300, Spain
ES002	(Name not given, since no consent given)	Santiago de Compostela , A Coruña 15706, Spain
ES003	(Name not given, since no consent given)	28046 Madrid, Spain
ES006	(Name not given, since no consent given)	Lugo, 27373, Spain
ES007	(Name not given, since no consent given)	15006 La Coruña, Spain
FR001	(Name not given, since no consent given)	Belfort Cedex, 90016, France
FR002	(Name not given, since no consent given)	Murs-Erigne, 49610, France
FR003	(Name not given, since no consent given)	Nântes, 44300, France
FR004	(Name not given, since no consent given)	Marseille, 13009, France
GB001	(Name not given, since no consent given)	West Midlands, B91 2JL, United Kingdom
GB003	(Name not given, since no consent given)	London, W12 0HS, United Kingdom
GB004	(Name not given, since no consent given)	Swansea, SA6 6JA, United Kingdom
GB006	(Name not given, since no consent given)	Manchester, M23 9LT, United Kingdom
GB009	(Name not given, since no consent given)	London, SW20 0NQ, United Kingdom
PL002	(Name not given, since no consent given)	Warszawa, 02-118, Poland
PL004	(Name not given, since no consent given)	Lodz, 91-002, Poland

5 PUBLICATION OF TRIAL RESULTS IN MEDICAL JOURNALS

The results of the KF5503/42 clinical trial have been published in the following medical journal:

Steigerwald I, Müller M, Kujawa J, Balblanc J-C, Calvo-Alén J. Effectiveness and safety of tapentadol prolonged release with tapentadol immediate release on-demand for the management of severe, chronic osteoarthritis-related knee pain: results of an open-label, Phase 3b study. J Pain Res 2012; 5: 121-38.