Trial number	KF5503/43
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 severe chronic pain due to osteoarthritis of the knee taking WHO Step III analgesics but showing a lack of tolerability.
EudraCT number.	2009-010425-39
Publication number	847022
Development phase	Phase IIIb
Investigational medicinal products	Tapentadol hydrochloride PR and tapentadol hydrochloride 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] Solihull West Midlands, B91 2JL, United Kingdom [redacted]
Trial period	First subject enrolled: 02 Oct 2009 Early trial termination: 10 June 2010 Last subject completed: 12 Aug 2010
Trial design	Multicenter, multinational, open-label, effectiveness Phase IIIb trial.
Trial centers	12 sites: 2 in Australia, 2 in Denmark, 4 in Germany, 2 in Poland, 1 in Spain, and 1 in the United Kingdom.

Objectives:

The primary objective was to evaluate the effectiveness, tolerability, and safety of tapentadol hydrochloride prolonged release (PR) in subjects with chronic pain due to osteoarthritis of the knee pretreated with WHO Step III opioids but showing lack of tolerability.

The secondary objectives were to:

- Evaluate equipotency ratios of tapentadol hydrochloride PR and different WHO Step III analgesics calculated using morphine-equivalent doses.
- Evaluate the conversion of subjects from previous WHO Step III analgesics to tapentadol hydrochloride PR.
- Evaluate the titration of tapentadol hydrochloride PR in clinical practice.
- Evaluate a potential reduction in the need for WHO Step I analgesics and co-analgesics under tapentadol hydrochloride PR treatment (sparing effect).

- Evaluate a potential reduction in the need for medications (anti-emetics and laxatives) to treat opioid-related adverse events in subjects previously treated with WHO Step III opioid analgesics.
- Evaluate the efficacy and tolerability of tapentadol hydrochloride PR versus previous treatment for osteoarthritis pain.
- 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	Expiration date
	50 mg	103M06	04/2011
	50 mg	103M08	04/2011
	100 mg	101M08	04/2011
	100 mg	102A05	06/2012
	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	101L18	09/2010
	250 mg	102L06	09/2010
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	Expiration date
	50 mg	104M06	01/2011
Composition:	Each IR tablet contains 58 mg tapentadol hydrochloride corresponding to 50 mg tapentadol free base		
Administration:	Oral, as needed		

Treatments:

Tapentadol hydrochloride PR

All subjects started the treatment with tapentadol hydrochloride PR (50 mg, 100 mg or 150 mg twice daily), if eligible, the morning after completing the Baseline Visit. The starting doses of tapentadol hydrochloride PR depended on the previous morphine equivalent daily dose (calculated on the basis of the previous dose of sustained and immediate release WHO Step III analgesics). The previous WHO Step III analgesic regimen was continued until the evening of the day of the Baseline Visit.

Tapentadol hydrochloride IR

Tapentadol hydrochloride immediate release (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 (pain due to osteoarthritis of the knee):
  - 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 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.

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 III 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 investigational medicinal product (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 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 withdrawals, and functionality. Adverse events associated with analgesics and co-analgesics, if applicable, were recorded.

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

All WHO Step III and potential concomitant 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 attended the site at Visit 1 and Visit 5, and were contacted by telephone at Visits 2, 3, and 4. Adverse events, concomitant medication taken and key parameters of functionality and quality of life were recorded at the visits.

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. 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 hydrochloride PR plus IR inclusive).

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

Data collected:

Primary endpoint

The primary endpoint was defined as responder rate 1, the percentage of subjects with the same or less pain (on the numerical rating scale [NRS-3]) at Week 6 compared with Week -1.

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.
- 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 III analgesics (Substudy B).
- Calculation of equipotent doses between Week -1 and Week 6:
  - Of total daily doses of tapentadol hydrochloride to previously used total average daily doses of WHO Step III analgesics.
  - Of total daily doses of tapentadol hydrochloride PR to previously used total average daily doses of prolonged release WHO Step III analgesics.

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

- Responder rate 1, defined as the percentage of subjects with the same or less pain (on the NRS-3) compared with Week -1 on the 11-point NRS-3.
- Responder rate 2, defined as the percentage of subjects with the same or less pain compared with Week -1 on the 11-point NRS-3 and an improvement of at least 1 category on the subject's satisfaction with treatment (5-point verbal rating scale).
- Change of the average pain intensity score on an 11-point NRS-3.
- Western Ontario McMaster Questionnaire scores.
- Patient's Global Impression of Change.
- Clinician's Global Impression of Change.
- Sleep Evaluation 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 analgesics and co-analgesics (comparison of Week -1 with Week 6, Week 8, and Week 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 IMPs as judged by the investigator.
- Cumulative adverse events (all adverse events throughout the trial cumulated separately during Week -1 prior to start of IMPs 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 (in case 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.
- Adverse events associated with the previous WHO Step III analgesic in Week -1 described as the underlying reason for converting to tapentadol hydrochloride.

Statistical methods:

The primary analysis was performed on the Per Protocol Set, which consisted of all enrolled subjects who received treatment at least up to and including Week 6, and had no major protocol deviations.

In addition, the analysis was carried out for the Main Analysis Population, which consisted of all enrolled subjects who received at least 1 dose of the IMPs and had at least 1 post-baseline pain assessment.

The primary null hypothesis tested for the trial was that the responder rate 1 (defined per subject as at most the same pain intensity at Week 6 compared with Week -1) was less than at least 60%.

The alternative hypothesis was that the responder rate 1 was at least 60%, i.e., the treatment with tapentadol hydrochloride PR was non-inferior to the previous treatment. The assumed non-inferiority margin was 14.3%.

For the primary efficacy variable, descriptive statistics were presented. It was analyzed using the lower limit of the observed 1-sided 95% confidence interval. Treatment effects and 95% confidence intervals were presented for the responder rate 1 at Week 6.

A descriptive comparison of all secondary endpoints was made for the defined stable treatment weeks.

An interim analysis was planned after about 50% of the subjects (based on n = 180 entered) had completed the trial. No adaptation of the trial was planned.

Sample size determination:

A standard deviation of 3 for a change in pain intensity score was assumed from earlier trials with tapentadol hydrochloride PR.

It was assumed that 70% of the subjects entered were eligible for the Per Protocol Population.

A sample size of N = 178 was required to perform all tests in the stepwise manner, given the rejection of the null hypothesis at the first 2 steps, as described in Section 12 of the protocol.

The targeted minimum number of subjects that would allow 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:

Originally, this trial was supposed to enroll 180 subjects. It was prematurely terminated after the recruitment of 82 subjects due to slow recruitment and a lack of IMP. The subject disposition and the reasons why subjects dropped out in the Observation Period, the Titration and stabilization Period, and the Optimal dose and Continuation Periods are depicted in the following 2 tables. Fifty-five subjects completed 6 weeks and 54 subjects completed 12 weeks of treatment. All subjects who were enrolled to Substudy A or B completed the substudies.

Number of subjects planned	180
	n (%)
Number of subjects enrolled	82 (100%)
Safety Set	63 (76.8%)
Main Analysis Population	62 (75.6%)
Per Protocol Set	53 (64.6%)
Substudy A Set	21 (25.6%)
Substudy B Set	21 (25.6%)

n = number of subjects with data available, percentage based on the number of subjects enrolled.

	Reason for discontinuation				
	Adverse events	**Lack of efficacy**	**Deaths**	**Other reasons**	**Total**
All subjects enrolled (N = 82)					
Observation Period	0	0	0	19 [a, b]	19
Safety Set (N = 63)					
Titration and Stabilization Period	5	2	0	1 [a]	8
Optimal Dose and Continuation Periods	1	0	0	0	1

a) One subject with a withdrawal of informed consent.
b) Includes 18 subjects who did not meet inclusion criteria or met exclusion criteria, were considered ineligible, satisfied with their previous treatment, suspected acute right heart syndrome, scheduled for surgery, screening failure, abdominal finding in physical examination: epigastric pain, subject younger than 40 years, no side effects.
N = Number of subjects.

Demographics:

A total of 63 subjects (37 women and 26 men) were included in the clinical trial in the Safety Set; all subjects were white. Subjects presented with a mean weight of 87.98 kg, a mean body mass index [BMI] of 31.28 kg/m^2, a mean age of 65.4 years, and a mean height of 167.4 cm.

Questionnaire related to the history and treatment of osteoarthritis-related knee pain:

The mean duration of osteoarthritis-related knee pain for all subjects in the Safety Set was 6.45 years with a wide range of 0.3 years to 20.7 years; the mean time to the first visit/consultation of a physician because of this pain was 5.03 months (range 0.0 to 48.0 months).

The osteoarthritis-related knee pain imposed a considerable burden to the subjects. On average, they had visited 1.86 physicians (maximum 6) since their pain started, consulted their physician once a month (mean number of 2.56 visits in the last 3 months, maximum 12), and had 0.48 unplanned consultations within the last 3 months. Eleven subjects (17.5%) were also hospitalized up to 3 times due to their severe osteoarthritis-related knee pain due to lack of efficacy of previous treatment/unbearable pain, or up to 2 times due to side effects of previous treatment or due to both reasons at the same time.

Subjects had taken up to 9 different analgesics regimens since their pain started (average 3.52). Five subjects (7.9%) took the WHO Step III analgesic buprenorphine (transdermal system) as prior medication. During Week -1, all subjects took WHO Step III analgesics as requested per protocol; buprenorphine was used in 77.8% of subjects at a mean release rate of about 20 µg/h corresponding to a morphine equivalent dose (MED) of 51.50 mg.

Most subjects had changed their regimen for their previous, second previous, or third previous regimen due to either a lack of efficacy or due to adverse events. Adverse events were the major reasons for a therapy switch from third previous to second previous and from second previous to the most recent regimen.

Since the osteoarthritis-related knee pain started, 7 subjects who were currently working were off work up to 3 times per year (mean 1.14 times) for up to 6 days per week (mean 1.14 days per week).

Prior medication:

Eighteen of 63 subjects (28.6%) reported the prior use of analgesics or co-analgesics that was stopped before or at the Screening Visit: WHO Step I analgesics (mostly diclofenac, ketoprofen, and meloxicam) were used by 23.8% of subjects, Step II analgesics such as opioids (dihydrocodeine, codeine, tramadol, or the fixed-dose combination products tramadol hydrochloride/ paracetamol and codeine phosphate/paracetamol) by 22.2% of subjects, and the WHO Step III analgesic buprenorphine by 7.9% of subjects. Two subjects (3.2%) took co-analgesics and 1 subject (1.6%) a psychoanaleptic non-analgesic (no side effect) medication that was stopped prior to trial enrollment.

Medication intake during Week -1:

During Week -1, all subjects reported the use of analgesics or co-analgesics in their diary. WHO Step I analgesics (mostly diclofenac, paracetamol, ibuprofen and ketorolac) were taken by 52.4% of subjects. Most frequently reported were paracetamol, diclofenac (resinate), ibuprofen, ketoprofen, or metamizole sodium. Seven subjects (11.1%) took the WHO Step II analgesics tramadol, a fixed-dose combination product of tramadol hydrochloride/paracetamol, paracetamol/codeine, tilidine hydrochloride, or naloxone hydrochloride/tilidine hydrochloride. All subjects took WHO Step III analgesics as requested per protocol. Buprenorphine (transdermal system) was most frequently used (in 77.8% of subjects), followed by oxycodone (9.5%) or oxycodone hydrochloride (6.3%), morphine (4.8%), hydromorphone (3.2%) or hydromorphone hydrochloride (3.2%), and methadone (1.6%). Co-analgesics (mostly pregabalin or gabapentin) were used by 14.3% of subjects.

During Week -1, 39 subjects (61.9%) reported the use of non-analgesic medication.

Concomitant medication intake:

Overall, 39 subjects (61.9%) used concomitant analgesics or co-analgesics during the trial. WHO Step I analgesics were used concomitantly with the IMP by 55.6% of subjects (most frequently paracetamol, ketoprofen, diclofenac [resinate], ibuprofen, or metamizole [sodium]). The use of a WHO Step II analgesic was reported for 2 subjects (3.2%) (continued use of paracetamol/codeine or tramadol) and of a Step III analgesic (buprenorphine) for 1 subject (1.6%). Co-analgesics were used by 9 subjects (14.3%) (most frequently pregabalin and gabapentin). The pattern of use for co-analgesics and non-analgesic (no side effect) medication was similar to Week -1.

During treatment with tapentadol hydrochloride, 35 subjects (55.6%) reported the intake of side effect medication. This includes drugs taken for side effects related to previous opioids which were continued according to protocol. Most frequently reported were laxatives (in 14.3% of subjects) and others (in 47.6%).

All 63 subjects of the Safety Set had a non-treatment emergent adverse event as the underlying reason for their switch to the IMP.

Effectiveness evaluation:

Tapentadol hydrochloride PR was effective in reducing severe chronic osteoarthritis-related knee pain in subjects who responded to previous treatment with WHO Step III analgesics but who were not fully satisfied with their analgesic regimen and requested a change due to opioid-related adverse events (AEs).

An analgesic effect in the same order to the effect achieved by previous strong opioids (NRS-3 ≤5) was also obtained once subjects reached a stable dose of tapentadol hydrochloride PR. Fifty of 53 subjects (94.3%) of the Per Protocol Set had the same or less pain at Week 6 compared with Week -1 on the 11-point NRS-3 and were classified as responders at Visit 6 (analyses with last observation carried forward [LOCF] imputation). The outcomes in that respect were better than anticipated in the assumptions underlying statistics, and dropouts were significantly lower. Thus, a positive primary endpoint was reached although the trial was prematurely terminated and the number of subjects was low.

A total of 54 of 62 subjects (87.1%) were classified as responders at Visit 6 in the Main Analysis Population. The responder rate 1 increased from the Interim Visit to Visit 12 and was similar at Visit 9 to Visit 12 when subjects who tapered their concomitant Step I analgesics and co-analgesics in the Continuation Period were included into the analyses.

Despite being responsive to previous WHO step III opioid treatment, subjects still showed relevant additional improvements in pain intensity during the trial. At the Screening Visit, the mean (SD) pain intensity score in the Main Analysis Population (N = 62) was 4.6 (0.63). The mean pain intensity scores (11-point NRS-3) decreased over time from baseline to Visit 6. Once an optimal dose of tapentadol hydrochloride PR was reached, mean NRS-3 values remained between 2 and 3. At Visits 6, 8, and 12, mean (SD) changes from baseline were -2.2 (1.55), -2.6 (1.44), and -2.7 (1.26). The changes from baseline were statistically significant ($p < 0.0001$).

The Western Ontario McMaster 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.

Most responders needed no adjustment of their tapentadol hydrochloride PR dose (52 of 62 subjects [83.9%]) or only 1 adjustment (2 [3.2%]) to reach the minimum target of titration (same or less pain on the 11-point NRS-3 compared to baseline).

The mean (SD) final stable dose of tapentadol hydrochloride PR at Visit 6 for all subjects was 232.7 (145.37) mg/day (median 200 mg/day, range 100 mg/day to 500 mg/day). Most subjects were satisfied with a low tapentadol hydrochloride PR dose of 50 mg twice daily (23 subjects, 41.8%) followed by 100 mg twice daily (13, 23.6%) and 200 mg twice daily (10, 18.2%). Six subjects (10.9%) took 250 mg twice daily and 3 subjects (5.5%) 150 mg twice daily.

Most of the subjects (78.2%) did not need to be treated with additional tapentadol hydrochloride IR at Visit 6 and 16.4% took less than 50 mg per day.

Based on relevant sample sizes, equianalgesic dose ratios could be calculated versus buprenorphine and oxycodone and were largely in line with previous findings from Phase III trials. Further clinically relevant improvements of pain intensity were observed under treatment with tapentadol hydrochloride in this population of responders to strong opioids.

Rotation from strong opioids went well based on the chosen methodology with starting dose cohorts as can be concluded from a very low rate of withdrawal symptoms related to the stop of the previous opioids, a very low rate of premature termination rate, and high level of effectiveness.

In summary, despite premature termination and a low sample size, effectiveness of tapentadol was demonstrated in the target population of this trial with severe pain due to osteoarthritis of the knee responding to strong opioid analgesics.

Safety and tolerability:

Neither deaths nor pregnancies were reported in this trial. Two subjects (3.2%) experienced 5 serious AEs. Thereof, abdominal pain and chest pain were considered by the investigator as probably related to the IMP, although the sponsor considered them to be unlikely related.

The treatment emergent adverse events most frequently reported were diarrhea (in 8.6% of subjects), nausea (7.8%), dizziness (5.2%), constipation (4.3%), hyperhidrosis (4.3%), drug withdrawal syndrome (3.4%), and fatigue (3.4%). They are known adverse drug reactions (ADRs) of tapentadol.

Except for diarrhea, no adverse changes in intensity or frequency were observed.

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

Most of the AEs reported as the underlying reason for switching from other strong opioids were alleviated under treatment with tapentadol hydrochloride. The difference at Week 6, Week 8, and Week 12 compared with Week -1 was statistically significant for constipation, dry mouth, and nausea, and for fatigue at Week 8 and Week 12.

Generally, rotation from the previous opioids to tapentadol went well with only occasional reports of withdrawal symptoms linked to cessation of the previous opioid.

The rate of subjects discontinuing from the trial due to AEs was low (9.5%).

No new adverse reactions to tapentadol hydrochloride PR were identified.

Conclusion:

The results of this trial have to be interpreted under the consideration that it was an open-label trial which was prematurely terminated, and that the resultant number of subjects included was low.

Tapentadol hydrochloride was effective in subjects with severe pain due to osteoarthritis of the knee who switched from WHO Step III analgesics due to lack of tolerability, but were responding to their previous treatment.

The primary endpoint was reached despite premature closure of recruitment.

The evidence of effectiveness is based on 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 (pain intensity score, WOMAC Osteoarthritis Index, quality of life parameters).

Based on relevant sample sizes, equianalgesic dose ratios could be calculated versus buprenorphine and oxycodone and were largely in line with previous findings from Phase III trials.

Further clinically relevant improvements of pain intensity were observed under treatment with tapentadol hydrochloride in this population of responders to strong opioids.

Rotation from strong opioids went well based on the chosen methodology with starting dose cohorts as can be concluded from a very low rate of withdrawal symptoms related to the stop of the previous opioids, a very low rate of premature termination rate and high level of effectiveness.

Most of the adverse events reported as the underlying reason for switching from other strong opioids were alleviated under treatment with tapentadol hydrochloride.

In this trial, tapentadol hydrochloride PR and IR have been administered simultaneously for the treatment of osteoarthritis -related knee pain and the AE profile was similar to that of Phase III trials in the same indication with similar treatment duration of tapentadol hydrochloride PR.

The safety profile of tapentadol hydrochloride in this trial was similar but with lower frequencies of treatment emergent AEs and fewer premature terminations than in previous trials with tapentadol hydrochloride IR and PR. Most of the AEs reported as the underlying reason for switching from other strong opioids improved after treatment with tapentadol hydrochloride.

The low discontinuation rate can be interpreted in line with tolerance to opioid-related side effects and low average daily doses used compared with previous Phase III trials in the same indication.

ICTR SYNOPSIS SUPPLEMENT

KF5503/43

Original ICTR issue date:	03 Aug 2011	**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 were 2 amendments to the protocol.

The following changes were documented in Amendment 01 (dated 18 Dec 2009):

- In order to adhere to the Danish guidelines for contraception, according to which double barrier methods are not acceptable, the double barrier methods in the list of methods of birth control in inclusion criterion 2 were not considered applicable for Denmark, but were still valid for other countries participating in the trial. This modification was only valid for this country.
- A further modification made was a change of the person signing as Operative Trial Coordinator to reflect the current composition of the protocol team.

This amendment was considered non-substantial and implemented after approval by the study team.

The following changes were documented in Amendment 02 (dated 09 Jun 2010):

- The wording for the duration of morning stiffness in inclusion criterion 5 that had been mistakenly stated in the original protocol was corrected.
- 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 WOMAC was replaced by the version for UK, resulting in a modification of the wording.
- The scales in the Hospital Anxiety and Depression Scale questionnaire were corrected according to the original version for the UK which were supplied by the license holder and were used by all patients.
- Improvement of the clarity and the consistency between the relevant protocol sections.

This amendment was considered substantial and implemented after approval by the competent authorities and independent ethics committees.

3 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
AU002	(Name not given, since no consent given)	Shenton Park, WA 6008, Australia
AU004	(Name not given, since no consent given)	Heidelberg West, 3081 Australia
DE001	(Name not given, since no consent given)	14089 Berlin, Germany

Site number	Investigator	Site address
DE002	(Name not given, since no consent given)	26789 Leer, Germany
DE007	(Name not given, since no consent given)	98746 Katzhuette, Germany
DE009	(Name not given, since no consent given)	39261 Zerbst, Germany
DK002*	(Name not given, since no consent given)	5000 Odense, Denmark
DK003	(Name not given, since no consent given)	DK-7100 Vejle, Denmark
DK007	(Name not given, since no consent given)	2650 Hvidovre, Denmark
ES001*	(Name not given, since no consent given)	46014 Valencia, Spain
ES004	(Name not given, since no consent given)	28046 Madrid, Spain
GB001	(Name not given, since no consent given)	Leeds LS9 7TF, United Kingdom
GB008*	(Name not given, since no consent given)	Middlesbrough TS4 3BW, United Kingdom
PL004	(Name not given, since no consent given)	20-093 Lublin, Poland
PL005	(Name not given, since no consent given)	07-300 Ostrow Mazowiecka, Poland

*Indicates sites that did not enroll subjects.

4 PUBLICATION OF TRIAL RESULTS IN MEDICAL JOURNALS

The results of the KF5503/43 clinical trial have been published in the following medical journal:

Steigerwald I, Schenk M, Lahne U, Gebuhr P, Falke D, Hoggart B. Effectiveness and tolerability of tapentadol prolonged release compared with prior opioid therapy for the management of severe, chronic osteoarthritis pain. Clin Drug Invest 2013; 33 (9): 607-19.