2 SYNOPSIS

Trial number	KF5503/45
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 nociceptive, mixed or neuropathic low back pain taking WHO Step III analgesics but showing a lack of tolerability.
Trial design	Multicenter, multinational, open-label, effectiveness Phase IIIb
Development phase	Phase IIIb
EudraCT number	2009-010428-25
Publication number	835093
Indication	Chronic nociceptive, mixed or neuropathic low back pain
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany
Coordinating investigator	[redacted] 13353 Berlin, Germany
Trial sites	28 sites: 1 in Australia, 4 in Belgium, 1 in Czech Republic, 2 in France, 7 in Germany, 2 in Poland, 4 in The Netherlands, 5 in Spain, and 2 in Switzerland.
Trial period	First subject enrolled: 30 Oct 2009 Early trial termination (last subject enrolled): 20 Oct 2010 Last subject completed: 21 Jan 2011

Objectives

The primary objective was to evaluate the effectiveness, tolerability, and safety of tapentadol hydrochloride prolonged release (PR) in subjects with severe chronic nociceptive, mixed or neuropathic low back pain (LBP) who were taking WHO Step III analgesics and showed lack of tolerability.

Secondary objectives in the population under study were to:

- Evaluate equipotency ratios of tapentadol hydrochloride PR and 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 whether the treatment with tapentadol hydrochloride PR could produce a reduction in the need for WHO Step I analgesics and co-analgesics (sparing effect).
- Evaluate whether the treatment with tapentadol hydrochloride PR could produce a reduction in the need for medications (antiemetics and laxatives) to treat opioid-related adverse events (AEs) in subjects previously treated with WHO Step III opioid analgesics.
- Evaluate the efficacy of tapentadol hydrochloride PR versus previous treatment for LBP with mixed and neuropathic origins.
- Evaluate the efficacy of tapentadol hydrochloride PR versus previous treatment in subjects with nociceptive LBP.
- Evaluate the efficacy of tapentadol hydrochloride PR in subjects with neuropathic or mixed versus nociceptive LBP.
- Evaluate the impact of tapentadol hydrochloride PR on function and quality of life parameters (subject-reported outcomes) in subjects with LBP.

Investigational medicinal products

Tapentadol hydrochloride PR

Substance code:	CG5503		
Substance name:	Tapentadol hydrochloride		
Batch numbers:	Dose	Batch	Expiration date
	50 mg	103M	Apr 2011
		103B	Dec 2012
	100 mg	101M	Apr 2011
		102A	Jun 2012
		101B	Feb 2013
	150 mg	102M	Mar 2011
		101B	Mar 2013
		101M	Mar 2011
		103M	Apr 2011
	200 mg	101L	Oct 2010
		102A	Jun 2012
		103A	Jun 2012
		101B	Feb 2013
	250 mg	103B	Dec 2012
		101L	Sep 2010
Composition:	Each PR tablet contained tapentadol hydrochloride 58.24 mg, 116.48 mg, 174.72 mg, 232.96 mg, 291.2 mg corresponding to the listed doses of 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	104M	Jan 2011
		105M	Feb 2011
		101A	May 2012
Composition:	Each IR tablet contained 58.24 mg tapentadol hydrochloride corresponding to the listed dose of 50 mg tapentadol free base		
Administration:	Oral, on demand, up to 2 tablets per day at least 4 hours apart.		

Treatments

Tapentadol hydrochloride PR

All subjects started the treatment with tapentadol hydrochloride PR (50 mg, 100 mg or 150 mg BID), if eligible, the morning after completing the Baseline Visit. Starting doses of tapentadol hydrochloride PR depended on the previous morphine equivalent daily dose (MED, calculated on the basis of the previous dose of sustained and immediate release [IR] WHO Step III analgesics). Subjects with an MED of up to 100 mg per day started with a dose of tapentadol hydrochloride PR of 50 mg BID, those with an MED of 101 mg to 160 mg per day with 100 mg BID, and those with an MED >160 mg per day with 150 mg BID. The previous WHO Step III analgesic regimen was continued until the evening of the day of the Baseline Visit.

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 appeared during the first days of titration after the previous treatment with an opioid had been stopped.

Tapentadol hydrochloride IR could be taken within the predefined regimen for incidental pain as needed throughout the trial (not exceeding a total daily dose of 500 mg tapentadol PR plus IR inclusive).

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

Trial population

The trial included men or non-pregnant, non-lactating women of at least 18 years of age with a diagnosis of chronic LBP requiring a strong analgesic (WHO Step III) who responded to previous

treatment with strong WHO Step III opioids but showed a lack of tolerability (i.e., opioid-related side effects and a rate of satisfaction with their previous analgesic regimen not exceeding "fair" on a subject satisfaction with treatment scale [5-point VRS])..

The painDETECT questionnaire was used to determine the likelihood of a neuropathic component of the LBP. Further characterization of the symptoms was performed in subjects with LBP in the painDETECT "unclear" or "positive" subsets. Subjects with a final score between 0 and 12 (scoring "negative") at the Screening and Baseline Visit were allocated to the nociceptive pain subset (likeliness of a neuropathic pain component little). Subjects with a score between 13 and 18 (i.e., scoring "unclear") at the Screening Visit and a "negative" score at the Baseline Visit or vice versa or those with an "unclear" score at both visits were allocated to the subset of subjects with LBP with a presumed neuropathic pain component. Subjects with a score between 19 and 38 (i.e., scoring "positive") at the Screening Visit or the Baseline Visit were allocated to the subset of subjects with a defined likelihood of a neuropathic pain component.

It was planned to enter at least 15% of subjects scoring "positive" in the painDETECT questionnaire and fulfilling diagnostic criteria for lumbar radiculopathy.

Methodology

This trial was a multicenter, multinational, open-label, effectiveness Phase IIIb trial including 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

This period started with the Screening Visit and ended with the Baseline Visit. The duration was shortened to 3 days if the lack of tolerability under the previous analgesic regimen was unbearable.

During the Observation Period, the general suitability of the subjects for the trial was determined.

The subject's pain intensity score during the last 3 days (using an 11-point numeric rating scale, [NRS-3]) and the non-treatment emergent adverse events (non-TEAEs) were recorded at the Screening Visit and the Baseline Visit.

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 investigational medicinal products (IMPs).

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

This period started after the Baseline Visit and finished at the end of Week 5.

The subjects went to the site at Visit 1 and Visit 5, and were contacted by telephone at Visit 2, Visit 3, and Visit 4. Adverse events, concomitant medication taken and key parameters of functionality and quality of life were recorded at the visits.

An interim telephone contact took place 3 days after starting the treatment with tapentadol hydrochloride PR to check if a dose adjustment was necessary. The amount of tapentadol hydrochloride IR taken by the subjects was considered for the dose adjustments with tapentadol hydrochloride PR.

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

The doses of WHO Step I analgesics and co-analgesics, as well as the 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

This period started at Week 6 and finished at the end of Week 8.

The 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) were 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

This period started after Visit 8 and ended with Visit 12 at the end of Week 12.

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

WHO Step I analgesics or co-analgesics of those subjects who consented were tapered without adjustment of the tapentadol hydrochloride PR and average tapentadol hydrochloride IR dose, to determine the sparing effect (Substudy A). If the pain score increased again, the dose prior to the last tapering step had to be reinstalled. Only 1 analgesic or co-analgesic could be tapered. Co-analgesics had priority regarding tapering.

Data collected and derived endpoints

Primary endpoint

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

Efficacy and quality of life endpoints

- Time to clinically relevant pain relief (at least the same pain intensity score on the 11-point NRS-3 compared to baseline).
- Time to effectiveness (time point at which improved tolerability and clinically relevant pain relief are reached or surpassed).
- Number of dose adjustments to clinically relevant pain relief and final stable dosage.
- Reduction of concomitant Step I analgesics and co-analgesics (Substudy A).
- Reduction in use of concomitant medication related to opioid-associated AEs of previous Step III analgesics (Substudy B).
- Calculation of equipotent doses between Week -1 and Week 6 (based on MED):

- Of total daily doses of tapentadol hydrochloride to previously used total average daily doses of WHO Step III analgesics (including additional doses of WHO Step II analgesics where concomitantly used).
- Of total daily doses of tapentadol hydrochloride PR to previously used total average daily doses of PR 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 to Week -1.
- Responder rate 2, defined as the percentage of subjects with the same or less pain compared to Week -1 and an improvement of at least 1 category on the subject's satisfaction with treatment (5-point verbal rating scale [VRS]).
- Change of the average pain intensity score on an 11-point NRS-3.
- Pain intensity (scores) in subjects with neuropathic or mixed LBP (referring to painDETECT subsets scoring "positive" or "unclear").
- Patient's global impression of change (PGIC).
- Clinician's global impression of change (CGIC).
- Sleep evaluation questionnaire (SQ) items.
- Short Form 36® (SF-36®) health survey scores.
- Subject's satisfaction with treatment.
- EuroQol-5 dimension (EQ-5D) scores.
- Hospital anxiety and depression scale (HADS).
- In neuropathic and mixed pain (painDETECT subsets scoring "positive" or "unclear"):
  - Short form McGill pain questionnaire (SF-MPQ).
  - Neuropathic pain symptoms inventory (NPSI).
  - Numeric rating scale-3 (NRS-3) for pain radiating towards or into the leg.
- Mean daily dose per compound of 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 AEs to previous, concomitant analgesic treatment and their causal relationship to the IMP as judged by the investigator.
- Cumulative AEs (all AEs throughout the trial cumulated separately during Week -1 prior to the start of the IMP and separately after the start of the IMP).
- Comparisons of the AEs that were present (ongoing and newly occuring) 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 AEs produced by previous analgesic treatment and tapentadol hydrochloride.
- Adverse events associated with previous WHO Step III analgesic in Week -1 described as the underlying reason for converting to tapentadol.

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 pain intensity score at Week -1 was the average pain intensity during the last 3 days (NRS-3) prior to start of intake of tapentadol PR. Pain intensity at Week 6 was the NRS-3 score taken at the end of Week 6. For subjects who prematurely discontinued the trial during the treatment period, the last observation carried forward (LOCF) was used as imputation method for missing values to calculate the NRS-3 score for the treatment period (Week 6).

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

The alternative hypothesis was that the response 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%.

The following selected secondary hypotheses were tested in a sequential manner if the null hypothesis for the primary endpoint was rejected. At each step, when the preceding null hypothesis failed to be rejected, further comparisons were not performed.

1. Test whether the response rate 2 (defined per subject as at most the same pain at Week 6 compared to Week -1 and an increase of at least 1 category on the subject's satisfaction with treatment from Week -1 to Week 6) was at least 60% with a non-inferiority margin of 14.3%.
2. Test whether the change from Week -1 of the average pain intensity (NRS-3) over Week 6 of the daily pain intensity was less than or equal to 0, i.e., the treatment with tapentadol hydrochloride PR was non-inferior to the previous treatment with a non-inferiority margin of 0.673.

For the primary efficacy variable, descriptive statistics were presented. It was analyzed in the Per Protocol Set using the lower limit of the observed 1-sided 95% confidence interval (Chi square test). Treatment effects and 95% confidence intervals were presented for the response rate 1 at Week 6.

Descriptive comparisons of all secondary endpoints were made for the defined stable treatment weeks.

Interim analysis

An interim analysis was performed after about 50% of the subjects (based on n = 180 entered) had completed the trial.

All analyses planned for the main part of the trial were carried out on this subset of subjects.

No adaptation of the trial was performed. The results of the interim analysis had no impact on the conduct of the trial.

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

Sample size determination

A standard deviation (SD) 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 Set.

For response criterion 1 and response criterion 2 and a non-inferiority margin of 14.3%, the lower limit of an observed 1-sided 95% confidence interval was expected to be above this margin with 80% power when the expected difference was 0, the expected discordant proportion 40% and the expected concordant proportion 60%, for a sample size of N = 125.

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 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 136 subjects due to slow recruitment and an overall shortness of IMP for the Phase IIIb program. The Safety Set comprised 125 subjects that were exposed to tapentadol hydrochloride PR. Eleven subjects prematurely terminated their participation in the trial during the Observation Period after withdrawal of informed consent, due to non-compliance, or other reasons (no intake of Step III analgesics; other pain conditions, no side effects and good treatment satisfaction with hydromorphone; no interest; laboratory findings; subject was re-screened; intensification of nausea needed new clinical evaluation; screened, failed exclusion criteria, hepatitis; pain score not according inclusion criteria; used tramadol).

The majority of subjects in the Safety Set (N = 82) had LBP with an “unclear” or “positive” likelihood of a neuropathic pain component. 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. One third of subjects of the Safety Set discontinued their trial participation between the Baseline Visit and the end of the Continuation Period, mostly due to AEs.

One hundred-two subjects completed 6 weeks and 93 subjects completed 12 weeks of treatment. All subjects who were enrolled to Substudy A or Substudy B completed the substudies.

Two subjects from the Safety Set were excluded from the Main Analysis Population (n = 123). Of all enrolled subjects, 69.1% comprised the Per Protocol Set.

	painDETECT Subset				
	"negative"	**"unclear"**	**"positive"**	**"unclear" or "positive"**	**Total**
Number of subjects planned					180
Subjects enrolled (N [%])	51 (100.0)	28 (100.0)	54 (100.0)	82 (100.0)	136 (100.0) [a]
Safety Set (n [%])	47 (92.2)	26 (92.9)	52 (96.3)	78 (95.1)	125 (91.9)
Main Analysis Population (n [%])	47 (92.2)	25 (89.3)	51 (94.4)	76 (92.7)	123 (90.4)
Per Protocol Set (n [%])	33 (64.7)	19 (67.9)	42 (77.8)	61 (74.4)	94 (69.1)
Substudy A Set (n [%])	6 (11.8)	6 (21.4)	11 (20.4)	17 (20.7)	23 (16.9)
Substudy B Set (n [%])	4 (7.8)	6 (21.4)	7 (13.0)	13 (15.9)	17 (12.5)

a) The painDETECT questionnaire was not available for 3 subjects.
N = Number of subjects in specified painDETECT subset, n = number of subjects allocated to the respective analysis population, % = percentage based on N.

	Reason for discontinuation (Safety Set) by painDETECT subsets				
Diagnosis of pain component	**"negative" (N = 47)**	**"unclear" (N = 26)**	**"positive" (N = 52)**	**"unclear" or "positive" (N = 78)**	**Total (N = 125)**
Number of subjects prematurely terminating the trial between baseline and Visit 12	13 (27.7)	7 (26.9)	12 (23.1)	19 (24.4)	32 (25.6)
Safety reasons not related to the IMP	0 (0.0)	1 (3.8)	0 (0.0)	1 (1.3)	1 (0.8) [a]
Adverse events	10 (21.3)	3 (11.5)	6 (11.5)	9 (11.5)	19 (15.2) [b]
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal of consent for any reason	3 (6.4)	0 (0.0)	2 (3.8)	2 (2.6)	5 (4.0)
Lost to follow up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lack of efficacy	0 (0.0)	2 (7.7)	3 (5.8)	5 (6.4)	5 (4.0)
Non-compliance	0 (0.0)	1 (3.8)	0 (0.0)	1 (1.3)	1 (0.8)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.3)	1 (0.8)

a) Subject [redacted] withdrew due to a serious treatment emergent adverse event (myocardial infarction) that was considered by the investigator to be not associated and not related to treatment with tapentadol hydrochloride and therefore rated as "safety reason not related to the IMP".
b) Subject [redacted] had the non-treatment emergent adverse event diabetes mellitus (pre-existing medical condition) that worsened during treatment with tapentadol and led to subject discontinuation from the trial. The investigator reported the non-treatment emergent adverse event diabetes mellitus as the reason for discontinuation. The worsening of diabetes was reported by the investigator as a treatment emergent adverse event. However, the countermeasure taken for it was reported as other action taken instead of discontinuation. This subject was therefore neither listed nor tabulated as a subject who prematurely discontinued the trial due to treatment emergent adverse events.
N = number of subjects in the category, IMP = investigational medicinal product.

Demographics:

Most of the subjects included in the Safety Set were white (99.2%), 1 subject was Asian. Subjects in all painDETECT subsets had similar body mass indices (mean 28.34 kg/m^2), but those in the painDETECT "positive" subset were slightly younger (mean 53.1 years) than those in the "unclear" (mean age 59.8 years) or "negative" subset (mean age 59.9 years). The percentage of women was higher in each subset and overall (60.8%).

History of low back pain:

The mean duration of LBP for all subjects in the Safety Set was 12.38 years; overall, the mean time to the first visit/consultation of a physician because of this pain was 11.32 months.

The neuropathic pain component imposed a considerable burden to the subjects. Subjects with an "unclear" or "positive" painDETECT score consulted their physician earlier (mean after 6.59 months, median 0.69 months) than subjects with a "negative" painDETECT score (after a mean of 19.06 months, median 2.00 months). They visited more doctors (mean 5.75) than subjects with a "negative" score (mean 4.79). Also, the number of consultations within 3 months was numerically higher at a mean of 3.30 in subjects with chronic LBP with an "unclear" or "positive" score compared to subjects with a "negative" score (mean 2.49).

More subjects with an "unclear" or "positive" painDETECT score had a history of hospitalization (69.2%) compared to subjects with a "negative" painDETECT score (48.9%). The overall number of hospitalizations (mean 5.72 versus 2.78), the number of hospitalizations due to lack of efficacy/unbearable pain and side effects of previous treatment (mean 5.09 versus 2.68), and the number of analgesics regimens since pain started (mean 6.38 versus 5.28) were higher in subjects with an "unclear" or "positive" painDETECT score. Despite that, the times per year of being off work due to pain since pain started was higher in subjects with a "negative" painDETECT score (mean 12.33 [n = 9] versus 3.43 [n = 14]).

Prior medication:

Only 15 of 125 subjects (12.0%) reported the use of analgesics or co-analgesics at the Screening Visit that was stopped before subjects were enrolled to the trial. World Health Organisation (WHO) Step I analgesics were used by 3 subjects (2.4%). Three subjects (2.4%) took WHO Step II analgesics: 2 subjects reported the intake of tramadol and 1 subject of tilidine. Only 10 subjects (8.0%) reported the use of WHO Step III analgesics (buprenorphine [hydrochloride], fentanyl, hydromorphone, morphine, oxycodone [hydrochloride]) as prior medication which was stopped prior to enrollment. The co-analgesics lidocaine hydrochloride, ropivacaine hydrochloride, or valproate sodium were used by 2 subjects (1.6%). Only 2 subjects of 125 (1.6%) reported the intake of a non-analgesic (no side effect) medication (psycholeptic or psychoanaleptic) that were stopped before subjects were enrolled to the trial.

Medication intake during Week -1:

Medication started prior to the Screening Visit but ongoing during Week -1 and medication started after the Screening Visit up to the Baseline Visit had to be documented as medication intake during Week -1. All subjects reported the use of at least 1 analgesics or co-analgesic medication during Week -1 in their diary.

The WHO Step I analgesics were taken by 60% of the subjects in the Safety Set. Most frequently reported were paracetamol, meloxicam, ibuprofen, metamizole, and diclofenac. The intake of analgesics/co-analgesics was highest in subjects in the painDETECT "positive" subset (69.2%).

Twenty-seven subjects (21.6%) took WHO Step II analgesics: 22 subjects reported the intake of tramadol and 3 subjects of tramadol/paracetamol containing products. One subject reported the intake of the fixed drug combination codeine/paracetamol, and 1 subject of naloxone HCl/tilidine HCl.

All but 2 subjects with a major protocol deviation (123 of 125, 98.4%) reported the use of WHO Step III analgesics during Week -1. Oxycodone (40 subjects) and naloxone HCl/oxycodone HCl (2 subjects), fentanyl (32 subjects), buprenorphine (27 subjects), morphine (20 subjects) were most frequently used followed by hydromorphone (10 subjects) and levomethadone or methadone HCl (1 subject each).

Co-analgesics were used by 66 subjects (52.8%). Most frequently used were pregabalin (in 22 [17.6%] of subjects), amytriptyline (16 subjects [12.8%]), gabapentin (13 subjects [10.4%]) and clonazepam (11 subjects [8.8%]). Subjects with LBP with an "unclear" painDETECT score (n = 26) were most frequently using co-analgesics (65.4%), mainly amytriptyline or pregabalin.

During Week -1, 110 subjects (88.0%) reported the use of non-analgesic medication, mainly drugs for acid-related disorders (38.4%), agents acting on the renin-angiotensin system (26.4%), lipid modifying agents (21.6%), and antithrombotic agents (20.0%). Furthermore, 59.2% applied at least 1 medication to treat side effects of opioid analgesics (laxatives and others). All side effect medication taken during Week -1 and related to non-TEAEs associated with analgesic or co-analgesic regimens had to be continued during treatment with tapentadol hydrochloride.

Concomitant medication:

Overall, 104 subjects (83.2%) used concomitant analgesics or co-analgesics during the trial, i.e., ongoing at the Baseline Visit or starting after the Baseline Visit or later up to and including Visit 12. The WHO Step I analgesics were used concomitantly with the IMP by 63.2% of subjects. Most frequently used were paracetamol, metamizole, and ibuprofen. The frequency of use was similar between the painDETECT subsets. Subjects in the painDETECT "positive" subset showed the highest concomitant use of WHO Step I analgesics (69.2%). The use of forbidden WHO Step II analgesics was reported for 4 subjects (3.2%): 1 subject took paracetamol/codeine; 2 subjects took tramadol, and 1 subject tramadol HCl/paracetamol. For 7 subjects (5.6%), the use of forbidden WHO Step III analgesics was reported: 2 subjects with buprenorphine (sublingual), 4 subjects with transdermal fentanyl, 3 subjects with morphine, 1 subject with nalbuphine, 2 subjects with pethidine HCl, and 1 subject with remifentanil.

Co-analgesics were used by 68 subjects (52.8%). Most frequently used were pregabalin (22 subjects, 17.6%), amitriptyline (16 subjects, 12.8%), gabapentin (13 subjects, 10.4%), and clonazepam (11 subjects, 8.8%). As required by the protocol, co-analgesics were supposed to be kept on a stable dose during the trial. The frequency was similar between the painDETECT subsets and the pattern of use during the trial was similar to Week -1.

The pattern of concomitant non-analgesic medication during Week 1 to Week 12 was similar to Week -1. Overall, 90.4% of subjects needed concomitant non-analgesic medication during the trial, mainly agents acting on the renin-angiotensin system (26.4%), antithrombotic agents (20.0%), beta blocking agents (19.2%), calcium channel blockers (12.0%), diuretics (15.2%), drugs for acid

related disorders (40.8%), drugs for obstructive airway diseases (12.8%), drugs used in diabetes (17.6%), lipid modifying agents (21.6%), psychoanaleptics (21.6%), psycholeptics (23.2%), and thyroid therapy (12.0%).

During treatment with tapentadol hydrochloride PR or IR, 60.8% of subjects reported the intake of side effect medication. This number also includes subjects that continued their side effect medication from Week -1. Most frequently reported were laxatives and others as in Week -1. The use of concomitant medication for side effect treatment was higher in subjects with an "unclear" (76.9%) or "positive" (67.3%) likelihood of a neuropathic pain component compared to subjects with "negative" likelihood (44.7%).

For 116 eligible subjects of the Safety Set (92.8%), non-TEAEs were considered by the investigators to be at least possibly associated to the intake of a WHO Step III opioid; additionally for 1 subject each to diclofenac, amitriptyline, or duloxetine.

For 37.6% of all subjects, TEAEs were assessed by the investigators as at least possibly associated to a prior analgesic/co-analgesic medication: to prior WHO Step III opioids in 34.4% of subjects, to Step I analgesics in 2.4%, and to co-analgesics in 4.0%.

Effectiveness evaluation (efficacy and quality of life parameters)

The analyses of effectiveness in this report included the primary analysis performed on the Per Protocol Set and the secondary analysis performed on the Main Analysis Population (the LOCF approach was applied in both analyses in cases of discontinuations or missing data at Visit 6). Further effectiveness analyses were performed on secondary endpoints. Additionally the subjects were grouped by combined diagnosis of pain component on which the primary, secondary, and further effectiveness analyses were performed.

A similar approach was followed in the effectiveness analyses of Substudy A and Substudy B.

It is known from the previous Phase IIIb trial in the same indication that painDETECT subsets may not be reliable in a population of responders to strong opioids. It can be assumed that part of the painDETECT "negative" subset would have turned "unclear" or "positive" if a washout had been performed. Therefore, results attributed to the painDETECT subsets have to be carefully assessed in this population.

Responder rates and pain intensity

Tapentadol hydrochloride PR was shown to be effective in subjects with severe chronic LBP with a nociceptive, presumed neuropathic, or defined neuropathic pain component who responded to previous treatment with strong WHO Step III opioids but showed a lack of tolerability (i.e., opioid-related side effects and a rate of satisfaction with their previous analgesic regimen not exceeding "fair" on a subject satisfaction with treatment scale [5-point VRS]).

An analgesic effect in the same order to the effect achieved by previous strong opioids (NRS-3 ≤5) was obtained once subjects reached a stable dose of tapentadol hydrochloride PR. Seventy-six of 94 subjects (80.9%) of the Per Protocol Set had the same or a lower pain intensity at Week 6 compared to Week -1 on the 11-point NRS-3 and were classified as responders (responder rate 1) at Visit 6 according to the analysis performed using the LOCF imputation method. This percentage was significantly higher than 60% for the overall trial population, with testing performed at 60% - 14.3%. A significant proportion of subjects maintained or improved the pain scores versus WHO Step III analgesics. Tapentadol hydrochloride PR showed to be non-inferior in subjects

successfully pre-treated with WHO Step III opioids. The 3 painDETECT subsets ("negative", "unclear", or "positive") also had significant responder rates 1. There was no statistically significant difference between the 3 painDETECT subsets or between subjects in the painDETECT "negative" subset (responder rate 1 of 81.8%) and the combined subset of "unclear" or "positive" painDETECT scores (80.3%).

Results for the primary endpoint are supported by the data obtained for the Main Analysis Population and by data collected for the secondary endpoints with/without using an imputation method.

In the Per Protocol Set, a total of 62 of 94 subjects (66.0%) had the same or a lower pain intensity at Week 6 compared to 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 VRS) from Week -1 to Week 6 (responder rate 2). They were classified as responders at Visit 6 (using the LOCF imputation). Subjects in the combined painDETECT "unclear" or "positive" subset showed a similar response rate 2 (65.6%) to subjects in the painDETECT "negative" subset (66.7%).

Despite being responsive to previous WHO Step III opioid treatment, subjects showed clinically relevant additional improvements in pain intensity under treatment with tapentadol hydrochloride. At the Screening and the Baseline Visit, the mean (SD) pain intensity score in the Main Analysis Population was 4.7 (0.80) and 4.8 (0.75), with a median at 5.0 and a range of 2 to 9 at both visits, demonstrating reasonable pain control by previous opioids. Between the Baseline Visit and the Interim Visit, the mean (SD) for all subjects increased to 5.2 (1.43), thereafter, there was a reduction in the pain intensity score up to Visit 5. In the maintenance phase (Optimal Dose and Continuation Periods), mean NRS-3 values remained between 3.7 and 4. At Visit 6, the mean (SD) change from baseline for all subjects in the Main Analysis Population was -0.9 (1.89), at Visit 8 it was -1.1 (1.91), and at Visit 12 it was -1.0 (2.02).

Tapentadol dosing in relevant subsets and related conclusions

Most responders needed no adjustment of their tapentadol hydrochloride PR dose (70 subjects [56.9%]) or only 1 adjustment (13 [10.6%]) up to the day of Visit 6. Eleven subjects (manually calculated) had 2 to 4 dose adjustments.

The mean (SD) final stable dose of tapentadol hydrochloride PR at Visit 6 for all evaluable subjects (n = 101) was 322.8 (120.73) mg/day (median 300 mg/day, range 100 mg/day to 500 mg/day). There was no significant difference between the painDETECT subsets. The final stable dose for subjects was 321.5 (124.36) mg/day for the treatment of LBP in subjects in the combined painDETECT "unclear" or "positive" subset and was apparently similar to that for subjects in the painDETECT "negative" subset (325.0 [115.57] mg).

Nine of 101 subjects (8.9%) were satisfied with a low tapentadol hydrochloride PR dose of 50 mg BID, 22 subjects (21.8%) with 100 mg BID. Twenty-two subjects (21.8%) took 150 mg BID, 33 subjects (32.7%) took 200 mg BID, and 15 subjects (14.9%) 250 mg BID.

About half of all evaluable 101 subjects (54.5%) did not take any additional tapentadol hydrochloride IR in the last 3 days prior to the Visit 6. The mean (SD) dose of tapentadol hydrochloride IR at Visit 6 was 24.6 (32.96) mg/day. Subjects in the painDETECT "negative" subset required a mean dose of 25.9 mg/day, subjects in the painDETECT "unclear" subset 20.8 mg/day, and subjects in the painDETECT "positive" subset 25.2 mg/day.

The mean daily dose of co-analgesics, if taken at all, in general remained stable as required per protocol.

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

Quality of life 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. But there was no clear difference between subjects scoring painDETECT "negative" and subjects scoring painDETECT "unclear" or "positive". Subjects were satisfied with the new treatment they received. Clinician's and patient's global impression of the change introduced by the new treatment was generally very good. Results were similar with LOCF imputation of missing data for Visit 6, Visit 8, and Visit 12, or when data from subjects who participated in Substudy A were included in the analyses.

At baseline, 38.2% of the subjects classified their overall quality of sleep as fair, 26.8% as good, 28.5% as poor, and 3.3% as excellent. At Visit 6, 31.4% of the subjects rated their overall quality of sleep as improved compared to baseline, 54.9% as no change and 12.7% as worsening. Similar results were reported at Visit 8 (34.4%, 51.0% and 13.5%) and Visit 12 (38.6%, 44.3% and 15.7%).

For most of the individual health domain scales of the SF-36, there were statistically significant changes in the mean scores from baseline to Visit 6, Visit 8, and Visit 12 indicating an increase in subjects' general health status.

At Visit 6, 2.0% of 102 subjects with data available rated their level of satisfaction as "excellent", 24.5% as "very good", and 46.1% as "good", 20.6% as "fair", and 4.9% as "poor". The analysis of changes from baseline showed 75.5% of improvement at Visit 6, 80.2% at Visit 8, and 84.3% at Visit 12. Whereas subjects in the painDETECT "negative" subset remained at an overall improvement rate just below 80% up to Visit 12, treatment satisfaction had improved in more than 80% of subjects in the combined painDETECT "unclear" or "positive" subset at the end of the trial.

Patient's global impression of change improved during the subsequent visits. At Visit 6, 5 of 102 subjects (4.9%) reported that their overall condition had "very much improved", 28.4% reported that it had "much improved", and 46.1% reported minimal improvement. At Visit 8, the percentages were 6.3%, 34.4%, and 42.7%; at Visit 12, 7.1%, 34.3%, and 44.3%.

The clinicians' perception on the global impression of the change of their subjects improved during the subsequent visits in parallel. At Visit 6, for 4.9% of their subjects they reported "very much improved", for 38.2% "much improved", for 37.3% "minimally improved". The reports of "no change" dropped to 11.8%. At Visit 8, ratings were 5.2%, 42.7%, 36.5%, and 9.4%. At Visit 12, it was further improved with 7.1%, 44.3%, 34.3%, and 11.4%.

The mean EQ-5D index scores increased over time up to Visit 6 and remained stable thereafter, statistically different from baseline at all the time points of evaluation. The mean changes from baseline for all the subjects in the Main Analysis Population were 0.1467 at Visit 6, 0.1561 at Visit 8, and 0.1588 at Visit 12, statistically different from baseline at Visit 6, Visit 8, and Visit 12. The mean patient's health state assessment scores increased over time from baseline to Visit 12. Changes from baseline were statistically significant for all subjects at all the time points of

evaluation. The mean change from baseline for all the subjects in the Main Analysis Population was 5.5 at Visit 6, 10.0 at Visit 8, and 10.0 at Visit 12.

Parameters related to anxiety and depression

Subjects in the combined painDETECT "unclear" or "positive" subset showed a clinically relevant mean score for anxiety (8.5) and depression (8.9) on the HADS at baseline while subjects in the painDETECT "negative" subset were below the threshold of 7 (mean scores 5.9 and 6.2). This indicates again a higher level of suffering in the combined painDETECT "unclear" or "positive" subset (Neuropathic Pain Subset).

At Visit 6, Visit 8, and Visit 12, mean anxiety scores decreased clinically relevantly by -1.3, -1.8, and -1.9 in subjects in the combined painDETECT "unclear" or "positive" subset; a similar reduction of -1.0, -1.1, and -0.9 was oberved for the mean depression score.

Effectiveness in the Neuropathic Pain Subset –
Parameters related to neuropathic pain-associated symptoms

painDETECT

The mean baseline scores for painDETECT in the Main Analysis Population were 6.5 for subjects with a "negative" painDETECT score, 14.7 for subjects with an "unclear" painDETECT score, and 21.1 for subjects with a "positive" painDETECT score. The mean scores and thus the likelihood of a neuropathic pain component of LBP decreased over time from baseline to Visit 12 in the "unclear" or "positive" painDETECT subset; changes were statistically different from baseline at Visit 6, Visit 8, and Visit 12.

Subjects in the combined painDETECT "unclear" or "positive" subset showed mean scores statistically different from baseline at Visit 6 (mean change -3.8), Visit 8 (-4.8), and Visit 12 (-4.0; excluding subjects who participated in Substudy A). Subjects in the painDETECT "negative" subset showed mean scores not different from baseline at any visit.

Many subjects who were classified as painDETECT "positive" at baseline had painDETECT "unclear" scores during treatment with the optimal tapentadol hydrochloride PR dose (Week 7 to Week 12); subjects scoring "unclear" at baseline now scored painDETECT "negative". Furthermore, statistically significant differences between the painDETECT subsets "negative" and "unclear" or "positive" were found at Visit 6, Visit 8, and Visit 12. The overall picture for the assessment of the painDETECT sub-scores was in line with the painDETECT final score.

painDETECT has so far not been validated to measure time course of individual parameters or the overall score in order to determine evolution over time or related treatment effects. However, results still indicate a high degree of symptom control related to neuropathic-pain-related signs and symptoms.

Neuropathic pain symptom inventory

The NPSI is validated to demonstrate time course and treatment effects in neuropathic pain populations.The mean NPSI scores in the combined painDETECT "unclear" or "positive" subset decreased over time from baseline to Visit 12. Changes were statistically different from baseline at Visit 6 and Visit 8 for all and at Visit 12 for most parameters. Results were of similar magnitude and clinical relevance applying LOCF imputation. They were also statistically significant at Visit 12 when subjects who participated in Substudy A were included into the analysis. This

behavior applied to the overall feeling score and the sub-scores burning pain, pressing pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia.

At baseline, most of the subjects had between 1 and 20 pain attacks in the previous 24 hours, namely, 13.2% with 11 to 20 pain attacks, 25.0% with 6 to 10 attacks, 36.8% with 1 to 5 pain attacks, 7.9% with more than 20 pain attacks, and 10.5% with no pain attacks. The frequency of pain attacks decreased during the trial, and by Visit 12, the number of subjects with 1 to 5 pain attacks was 28.6% and with no pain attacks had increased to 26.2%.

Radiating pain towards or into the leg

In subjects with LBP in the combined painDETECT "unclear" or "positive" subset, the mean (SD) pain intensity score for pain radiating towards or into the leg was 4.5 (1.97) at baseline and decreased significantly in the subsequent visits to a final value of 3.8 (2.21) at Visit 12. Subjects with a positive diagnosis of lumbar radiculopathy (representing predominantly neuropathic back pain) had, as expected, a higher mean (SD) pain intensity score for pain radiating towards or into the leg of 4.9 (1.31) at baseline that decreased to reach 3.9 (2.03) at Visit 12.

Short form McGill pain questionnaire

In the combined painDETECT "unclear" or "positive" subset, the mean total scores for the SF-MPQ decreased over time from baseline (21.2) to Visit 12, statistically significant from baseline at all the time points of evaluation, i.e., to 14.7 at Visit 6, 14.0 at Visit 8, and to 16.4 at Visit 12. Significant reduction was also evident applying LOCF imputation or including subjects into the analysis who participated in Substudy A (reduction at Visit 12 to 14.5). Sensory scores, affective scores, pain scores, and present pain intensity scores measured for the SF-MPQ showed a similar behavior.

Effectiveness in the Substudy A Set

In Substudy A, 23 subjects tapered WHO Step I analgesics or co-analgesics without compromising the pain reduction obtained with tapentadol hydrochloride PR. All subjects completed Visit 12. Fifteen subjects (65.2%) accomplished a 100% reduction of their analgesic/co-analgesic medication: 6 subjects tapered their Step I analgesics to 100% (diclofenac or paracetamol in 2 subjects each, flupirtine or ketoprofen in 1 subject each) and 9 of 17 subjects their co-analgesic medication (amitriptyline or gabapentin in 2 subjects each, pregabalin in 4 subjects, and tolperisone in 1 subject). Five subjects achieved a partial tapering of their co-analgesics; duloxetine (1 subject) or pregabalin (2 subjects) could not be reduced without impairing pain relief.

The mean pain intensity scores (11-point NRS-3) decreased over time from baseline to Visit 12. At Visit 6, the mean change from baseline for all the subjects was -1.3, at Visit 8 it was -1.4, and at Visit 12 it was -1.9. At Visit 8, 78.3% of all subjects who entered Substudy A were considered responders (responder rate 1); the responder rate remained around 80% after Visit 8 and reached 87.0% at Visit 12. The overall responder rate 2 at Visit 8 was 73.9% and did not change during the tapering period. At Visit 12, it was 82.6%.

The mean stable dose of tapentadol hydrochloride PR at Visit 6 was 356.5 mg/day in Substudy A and was higher than for all subjects (322.8 mg/day) participating in the trial. The mean (SD) daily dose of tapentadol hydrochloride IR at Visit 6 was 21.7 (32.74) mg/day.

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

Despite the small sample size, the results indicate that tapentadol–because of its 2 mechanisms of action–can lead to a clinically relevant sparing of co-analgesics without impairing analgesia.

Additionally, an analysis deducting the results obtained between Week 8 and Week 12 for Substudy A participants from the overall dataset was performed to investigate a potential bias that might have occurred due to artificially introduced pain peaks in the tapering period. The analysis revealed that tapering of concomitant analgesic/co-analgesic medication had no clinically relevant impact on efficacy or quality of life parameters.

Effectiveness in the Substudy B Set

In Substudy B, 11 of 17 subjects (64.7%) accomplished a 100% reduction of concomitant medication (mostly laxatives or metoclopramide) related to opioid-associated AEs of previous Step III analgesics. Further 6 subjects achieved a reduction of the dose of 0% to 75% (no reduction in 4 subjects, 50.7% in 1 subject, and 75% in 1 subject). All subjects completed Visit 8 but 1 subject withdrew at Visit 8.

In general, results of the quality of life and effectiveness endpoints (SF-36, EQ-5D, satisfaction with treatment, PGIC, CGIC) for subjects participating in Substudy B were not different from those of the overall trial population. Effects observed at Visit 6 were maintained or further improved until Visit 8.

Safety and tolerability:

General adverse events

The TEAEs reported by the subjects treated with tapentadol in this trial were in line with its well-known safety profile.

Incidences of TEAEs were low with 68% of the subjects experiencing at least 1 TEAE (85 of 125 subjects). The incidence of the most common TEAEs (≥5%) included upper abdominal pain (5.6 %), constipation (12%), diarrhea (10.4%), dizziness (12.8%), dry mouth (6.4%), drug withdrawal syndrome (26, 20.8%), fatigue (10.4%), headache (14.4%), hyperhidrosis (8.0%), insomnia (12.8%) and nausea (15.2%).

Withdrawal syndrome (26 subjects, 20.8%) occurred mainly at the switch from the previous strong opioid to tapentadol and was reported mainly by 1 site (DE003). Insomnia was also mainly reported by the subjects of 1 site (DE003).

The overall prevalence of AEs (e.g., constipation, nausea, fatigue, somnolence, hyperhidrosis, dizziness) in the trial population that were reported as the most important reason to switch to tapentadol hydrochloride PR was reduced during this trial.

Thirty-two subjects did not complete the trial. Of these, 23 discontinued between baseline and Week 6 (Titration Period), and 9 between Week 6 and Week 12 (Maintenance Period).

One subject (0.8%) discontinued due to safety reasons not related to the IMP (a serious AE) and 19 subjects (15.2%) due to AEs. Subject 5053 had the non-TEAE diabetes mellitus (pre-existing medical condition) that worsened during treatment with tapentadol and led to subject discontinuation from the trial. The investigator reported the non-TEAE event diabetes mellitus as the reason for discontinuation. The worsening of diabetes was reported by the investigator as a TEAE however, the countermeasure taken for it was reported as other action taken instead of

discontinuation. This subject was therefore neither listed nor tabulated as a subject who prematurely discontinued the trial due to TEAEs.

Overall, the discontinuation rate (25.6%) was lower compared to a previous Phase IIIb trial (33.5%), conducted in subjects with LBP previously treated with WHO Step I or Step II analgesics or with no regular analgesics. The difference is probably due to the development of tolerance to opioid-related side effects. These results also indicate a successful rotation of opioid-tolerant subjects to tapentadol.

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.

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

Serious adverse events and deaths

Neither deaths nor pregnancies were reported in this trial.

In total, 21 serious AEs were reported in the trial.

Eleven subjects reported 19 serious TEAEs. Twelve serious TEAEs were considered not related or unlikely related to the IMP.

Two other subjects experienced 3 serious AEs which were not tabulated. One subject reported a serious TEAE that occurred after the completion of the IMP intake. The second subject had 2 serious non-TEAEs that occurred during the Observation Period, before IMP intake and did not qualify for the Safety Set.

Conclusion

The results of this trial have to be interpreted under the consideration that it was an open-label trial which was prematurely terminated.

Tapentadol hydrochloride was effective in subjects with severe chronic LBP with a nociceptive, presumed, or defined neuropathic pain component who switched from WHO Step III analgesics due to lack of tolerability, but were responding to their previous treatment.

Rotation from strong opioids went well based on the chosen methodology with starting dose cohorts as can be concluded from a low rate of premature termination and high level of effectiveness.

The primary endpoint was reached despite premature closure of recruitment.

The evidence of effectiveness is based on a positive result of the primary endpoint (responder rate 1, same or a lower pain intensity at Week 6 compared to Week -1 on the 11-point NRS-3) and of the analysis of the secondary endpoints (e.g., responder rate 2, pain intensity score, quality of life parameters).

Based on relevant sample sizes, equianalgesic dose ratios could be calculated versus buprenorphine, fentanyl, oxycodone, hydromorphone, and morphine 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.

The results of the tapering of WHO Step I analgesics or co-analgesics indicate that tapentadol can elicit a clinically relevant sparing of these medications without impairing analgesia because of its 2 mechanisms of action.

The results of the reduction of concomitant medications related to opioid–associated AEs of previous Step III analgesics suggest that the achieved reductions do not impair the effectiveness of tapentadol, the treatment satisfaction or the quality of life of the subjects.

The prevalence of most of the AEs reported as the underlying reason for switching from other strong opioids was reduced under treatment with tapentadol hydrochloride.

The additional intake of tapentadol hydrochloride IR on top of tapentadol hydrochloride PR did not alter the AE profile of tapentadol, which was similar to that observed in Phase III trials with tapentadol hydrochloride PR in the same indication and similar treatment duration. However, the frequencies of TEAEs and premature terminations were lower than in previous Phase IIIb trials with tapentadol hydrochloride IR and PR combined.

Publications based on this trial

Steigerwald I, Hans G, Schäfer M, Cantagrel N, Falke D, Gálvez R. Equipotency of tapentadol and World Health Organization (WHO) Step III opioids for the management of severe, chronic low back pain—interim results from an open-label, Phase 3b study. Poster 062; Proceedings of the Networking World Anesthesia Convention (NWAC) World Anesthesia Congress, Rome, Italy, 11-15 Apr 2011.

Steigerwald I, Falke D, Gyllensvärd A, Gálvez R, Schäfer M. Equipotency of tapentadol prolonged release (PR) and World Health Organization (WHO) Step III opioids in patients with severe, chronic low back pain. Abstract A027; poster presented at 10th Annual American Society of Regional Anesthesia and Pain Medicine (ASRA) Pain Meeting and Workshop, New Orleans, Louisiana, United States; 17-20 Nov 2011.

ICTR SYNOPSIS SUPPLEMENT

KF5503/45

Original ICTR issue date:	16 Jan 2012	**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 02 amendments to the protocol.

The modifications in Amendment 01 were implemented to fulfill requirements from the Czech authorities and were only valid for the Czech Republic. The following changes were documented:

- The inclusion criterion referring to the duration of use of previous World Health Organization (WHO) Step III analgesic treatment was modified (prolonged from 2 weeks to 3 months).
- The amendment enlarged the subpopulation of subjects in whom a prolonged opioid response could be evaluated as basis for subsequent equipotency calculation versus tapentadol.
- Considering the fact that this population was already included within the overall trial population and the expected low number of subjects to be contributed from the sites in the Czech Republic relative to the overall trial population, no relevant impact on trial outcomes was expected.
- The person signing as Operative Trial Coordinator was changed to reflect the current composition of the protocol team.

Amendment 02 was implemented to correct the definition of typical dermatomal pain as diagnostic criterion for lumbar radiculopathy. The following changes were also documented:

- The number of signatories of the protocol was reduced to match current the updated standards of the sponsor.
- Clarification was provided on deviations from established visit windows in exceptional cases.
- The scales in the Hospital Anxiety and Depression Scale (HADS) questionnaire were corrected according to the original version for the United Kingdom.

Furthermore, this amendment included changes that improved the clarity and the consistency between relevant protocol sections.

3 INFORMATION REGARDING CLINICAL HOLD OR EARLY TERMINATION

This clinical trial was prematurely terminated after the recruitment of 136 subjects due to slow recruitment and an overall shortness of IMP for the Phase IIIb program.

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
AU002	(Name not given, since no consent given)	Western Australia 6001, Australia
BE001	(Name not given, since no consent given)	Liège B-4000, Belgium
BE002	(Name not given, since no consent given)	Edegem B-2650, Belgium
BE003	(Name not given, since no consent given)	Charleroi, B-6000 Belgium
BE004	(Name not given, since no consent given)	Brugge B-8000, Belgium
CH001	(Name not given, since no consent given)	Basel 4051, Switzerland
CH002	(Name not given, since no consent given)	St. Gallen, 9007 Switzerland
CZ001	(Name not given, since no consent given)	Brno 656 91, Czech Republic
DE001	(Name not given, since no consent given)	Berlin 13353, Germany
DE003	(Name not given, since no consent given)	Berlin 14089, Germany
DE004	(Name not given, since no consent given)	Leipzig 04229, Germany
DE005	(Name not given, since no consent given)	Albstadt-Ebingen 72458, Germany
DE006	(Name not given, since no consent given)	Kiel 24149, Germany
DE007	(Name not given, since no consent given)	Stuttgart 70178, Germany
DE008	(Name not given, since no consent given)	Leipzig 04103, Germany
ES001	(Name not given, since no consent given)	Granada 18014, Spain
ES003	(Name not given, since no consent given)	Málaga 29010, Spain
ES004	(Name not given, since no consent given)	Sevilla 41013, Spain
ES005	(Name not given, since no consent given)	Valencia 46010, Spain
ES006	(Name not given, since no consent given)	Cadiz 11009, Spain
FR001	(Name not given, since no consent given)	Toulouse 31059, France
FR004	(Name not given, since no consent given)	Thionville 57100, France
NL001	(Name not given, since no consent given)	Tiel 4002WP, Netherlands
NL002	(Name not given, since no consent given)	Alkmaar 1815 JD, Netherlands
NL003	(Name not given, since no consent given)	Eindhoven 5623 EJ, Netherlands
NL004	(Name not given, since no consent given)	Doetinchem 7009 BL, Netherlands
PL001	(Name not given, since no consent given)	Poznan 60-773, Poland
PL002	(Name not given, since no consent given)	Krakow 31531, Poland

5 PUBLICATION OF TRIAL RESULTS IN MEDICAL JOURNALS

The results of the KF5503/45 clinical trial have been published in the following medical journal:

Gálvez R, Schäfer M, Hans G, Falke D, Steigerwald I. Tapentadol prolonged release versus strong opioids for severe, chronic low back pain: results of an open-label, Phase 3b study. Adv Ther 2013; 30 (3): 229-59.