Trial number	KF5503/58
Title of trial	Evaluation of the effectiveness, safety, and tolerability of tapentadol PR versus a combination of tapentadol PR and pregabalin in subjects with severe chronic low back pain with a neuropathic pain component.
Trial design	Randomized, multicenter, multinational, double-blind, active-controlled, parallel-arm, Phase IIIb trial with an open-label run-in period in approximately 500 subjects.
Development phase	Phase IIIb
EudraCT number	2010-019998-14
Publication number	247251
Indication	Severe chronic low back pain with a neuropathic pain component.
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany
Coordinating investigator	[redacted] 24105 Kiel, Germany
Trial sites	48 sites: 12 in Germany, 10 in Poland, 5 in Belgium, 4 in Denmark, 8 in Spain, 5 in Austria and 4 in The Netherlands.
Trial period	First subject enrolled: 23 Mar 2011 Last subject completed: 17 Jan 2012

Objectives

Primary objective

The primary objective was to evaluate the effectiveness, safety, and tolerability of increasing doses of tapentadol prolonged release (PR, 300 mg per day after run-in, up-titration to 500 mg per day) versus a combination of tapentadol PR (300 mg per day after run-in) and pregabalin (titrated to 300 mg per day) in subjects requiring additional analgesia after titration to tapentadol PR 300 mg per day.

Secondary objectives

- To evaluate the impact of tapentadol PR and a combination of tapentadol PR and pregabalin on function and quality of life (QoL) parameters (subject-reported outcomes) in subjects with severe low back pain with a neuropathic pain component.
- To evaluate a subset of subjects satisfied with moderate doses of tapentadol PR (300 mg per day).
- To evaluate potential responder profiles based on neuropathic symptoms (painDETECT subscores).

Investigational medicinal products (IMPs)

Tapentadol hydrochloride PR

Substance name:	Tapentadol hydrochloride		
Batch number and expiration date:		Batch	Expiration date
	Tapentadol 50 mg PR2 tablets	KDIRC6	03/2013
	Tapentadol 150 mg PR2 tablets	KDNK54	03/2013
	Tapentadol 150 mg PR2 tablets	KDNK55	03/2013
	Tapentadol 200 mg PR2 tablets	KDGU69	03/2013
	Tapentadol 250 mg PR2 tablets	KDSP79	03/2013
	Tapentadol 50 PR2small tablets	103B	12/2012
	Tapentadol 100 PR2small tablets	101B	02/2013
	Tapentadol 150 PR2small tablets	101B	03/2013
Composition:	Each PR tablet contained tapentadol hydrochloride 58.24 mg, 116.48 mg, 174.72 mg, 232.96 mg, 291.20 mg corresponding to the listed doses of 50 mg, 100 mg, 150 mg, 200 mg and 250 mg tapentadol free base.		
Administration:	Oral		

Pregabalin

Substance name:	Pregabalin		
Batch numbers:		Batch	Expiration date
	Pregabalin 75 mg Capsules	E07727-002E01	07/2012
	Pregabalin 75 mg Capsules	E07727-038E01	08/2012
	Pregabalin 150 mg Capsules	E07727-003E01	07/2012
	Pregabalin 150 mg Capsules	E07727-039E01	09/2012
Composition:	Each hard capsule contains pregabalin 75 mg or 150 mg. Over-encapsulation by capsules Size 00.		
Administration:	Oral.		

Placebo matching pregabalin

Batch numbers:	**Batch**	**Expiration date**
	E07727-004E01	07/2013
Composition:	Hard gelatin capsules Size 00 containing microcrystalline cellulose, gelatin, titanium dioxide (E171), black iron oxide (E172).	
Administration:	Oral.	

Treatments

Titration Period

During the 3-week Titration Period, tapentadol PR was administered in an open-label fashion as follows:

- Starting at 2 x 50 mg per day (100 mg per day) after the Baseline Visit and titrated upwards in steps of 100 mg per day (2 x 50 mg) on a weekly basis.
- Allowing for weekly interim titration steps 3 days after a previous dose adjustment in case of a pain intensity requiring faster up-titration.
- Until a daily dose of 300 mg per day was reached (dose steps: 2 x 50 mg per day, 2 x 100 mg per day, 2 x 150 mg per day).

The dose of tapentadol PR 300 mg per day was maintained stable until the Randomization Visit. The Titration Period could be shortened to a minimum of 10 days in case of faster up-titration.

Comparative period

Subjects who qualified for randomization (had a reduction of at least 1 point on the NRS-3, did not report tolerability issues from tapentadol PR that would have prohibited further dose escalation or the addition of pregabalin, and reached a stable dose of tapentadol PR 300 mg per day), continued treatment in a double-blind fashion in 1 of the following 2 treatment arms in the Comparative Period:

Tapentadol PR 500 mg (TAP)

- After the Randomization Visit, the subjects continued their previous regimen of tapentadol PR 300 mg per day, to which 100 mg per day were added (total daily dose of 400 mg, provided in 2 tablets of 200 mg each).
- After Visit C1 (1 week after the Randomization Visit), the subjects continued their previous regimen of tapentadol PR 300 mg per day, to which 200 mg per day were added (total daily dose of 500 mg, provided in 2 tablets of 250 mg each).

Combination of tapentadol PR 300 mg per day with increasing doses of pregabalin (TAP+PREG)

- After the Randomization Visit, the subjects continued their previous regimen of tapentadol PR 2 x 150 mg per day plus pregabalin 2 x 75 mg (total daily dose of 150 mg pregabalin).
- After Visit C1 (1 week after the Randomization Visit), subjects continued their previous regimen (end of the Titration Period) of tapentadol PR 2 x 150 mg per day plus pregabalin 2 x 150 mg (total daily dose of 300 mg pregabalin).

Dose increases could be limited or slowed down depending on the subject's tolerability.

Subjects who did not qualify for randomization to the Double-Blind Treatment Period were discontinued from the trial at the Randomization Visit for the following reasons:

- They did not reach a reduction of at least 1 point on the NRS-3 at the Randomization Visit compared to the Baseline Visit, demonstrating lack of response to tapentadol PR.
- They reported adverse events caused by tapentadol PR, which prevented further dose increase or the addition of pregabalin (at the discretion of the investigator).
- They had not reached a stable dose of tapentadol PR 300 mg per day in the Titration Period.

Open-label Pick-Up Arm

The Open-Label Pick-Up Arm consisted of subjects who dropped out after randomization due to treatment emergent adverse events (TEAEs) at least possibly related to the IMPs and continued their stable treatment with tapentadol PR either 400 mg per day or 300 mg per day as target dose.

If subjects dropped out of the double-blind arms due to TEAEs at least possibly related to the IMPs after they had reached the maximum dose levels (TAP per day, or tapentadol PR 300 mg per day plus pregabalin 300 mg per day), they were allowed to continue their treatment in the Open-Label Pick-Up Arm at a stable dose of tapentadol PR 400 mg per day (if not limited by ongoing tolerability issues). If a lack of tolerability was also reported in the Open-Label Pick-Up Arm, their doses could be lowered ad interim to tapentadol PR 300 mg per day.

If subjects experienced an unbearable TEAE (considered at least possibly related to the IMPs) on the next dose levels after the Randomization Visit (tapentadol PR 400 mg per day, or tapentadol PR 300 mg per day plus pregabalin 150 mg per day), they could be assigned to the Open-Label Pick-Up

Arm and were treated with a stable dose of tapentadol PR 300 mg per day or 400 mg per day (if not limited by ongoing tolerability issues).

Open-label Continuation Arm

The Open-Label Continuation Arm consisted of subjects who did not qualify for randomization to the Double-Blind Treatment Period, continued the trial on a stable dose of tapentadol PR 300 mg per day (open label) until the Final Evaluation Visit if they had already reached a satisfactory level of pain relief (11-point numeric rating scale during the last 3 days [NRS-3] at the Randomization Visit <4; first cohort).

Trial population

Subjects with a diagnosis of chronic low back pain (defined as pain lasting for at least 3 month) that required a strong analgesic (World Health Organization [WHO] Step III) as judged by the investigator and scored positive or unclear on the painDETECT diagnostic screening questionnaire at the Baseline Visit.

Methodology

The trial included:

Enrollment/Washout Period (open-label): from Enrollment Visit until 1 day prior to the Baseline Visit

At the Enrollment Visit, the inclusion and exclusion criteria were checked to evaluate the subject's eligibility for the trial. Blood and urine samples were taken and the questionnaires were answered.

Subjects scoring positive or unclear on the painDETECT questionnaire were enrolled. Also, subjects scoring negative but with a painDETECT score of at least 9 were enrolled if they had been pretreated with a stable regimen of centrally acting analgesics and/or co-analgesics (that had to be washed out). These subjects were expected to score positive or unclear on the painDETECT questionnaire to a high extent after washout of their centrally acting (co-)analgesic regimens which were expected to suppress neuropathic pain symptoms.

Washout Period (if applicable):

- Three days up to 2 weeks (during Week -2 and Week -1).
- The duration of the Washout Period –if any– and (down-) tapering steps depended on previous opioid analgesics and co-analgesics and their respective doses.
- WHO Step I analgesics were maintained at a stable dose.

For subjects who did not need to washout their previous analgesic treatment, a Baseline Visit was scheduled as soon as clinical laboratory monitoring results were available.

Titration Period (open-label): from the Baseline Visit until 1 day prior to the Randomization Visit (3 weeks)

Only subjects scoring positive or unclear on the painDETECT questionnaire at the Baseline Visit were entered.

Furthermore, diagnostic examination for lumbar radiculopathy was performed according to the following specifications at the Baseline Visit:

- Typical dermatomal pain.
- Radiating beyond the knee towards the foot (sciatica).
- Evoked by stretching of the sciatic nerve.

and

- Signs of root dysfunction (at least 1 of the following):
- Sensory impairment, motor symptoms from compression of lumbar nerve root (L4, L5, S1) and/or
- Absent or diminished reflexes related to affected dermatome(s), e.g., quadriceps femoris or triceps surae reflexes.
- Sensory deficits in the affected painful dermatomal area, demonstrated by quantitative sensory testing (QST).

Comparative Period (double-blind): from the Randomization Visit until the Final Evaluation Visit (8 weeks)

Subjects were eligible for randomization in the Comparative Period if:

- They responded to tapentadol PR (NRS-3 pain intensity score decrease of at least 1 point between the Baseline Visit and the Randomization Visit).
- They had reached an NRS-3 pain intensity score of 4 or greater (NRS-3 ≥4) at the Randomization Visit.

Subjects who were not eligible for randomization were entered in the Open-Label Continuation or discontinued from the trial.

Follow-up Period (blinded tapering down/out of IMP in Week 12 and Follow-up Visit [2 weeks; Week 12 to Week 13])

Tapering down/out of IMPs was performed according to their summary of product characteristics.

Data collected

Primary endpoint

The primary endpoint was defined as the comparison of TAP and TAP+PREG regarding the change in NRS-3 pain intensity scores from the Randomization Visit to the Final Evaluation Visit.

Efficacy and quality of life endpoints

- Change of the pain intensity score on an 11-point NRS-3.
- painDETECT score.
- Numeric rating scale-3 pain intensity scores for pain radiating towards or into the leg.
- Worst pain (11-point NRS) during the last 24 h prior to the assessment visit.
- Subject’s satisfaction with treatment (5-point rating scale).
- Patient’s global impression of change (PGIC).
- Clinician’s global impression of change (CGIC).
- Neuropathic pain symptoms inventory (NPSI).
- Sleep evaluation questionnaire (SQ) items.

- Hospital anxiety and depression scale (HADS).
- Short form-12® health survey (SF-12®) scores.
- EuroQol-5 dimension (EQ-5D) scores.

Main descriptive comparisons were performed for these endpoints collected at the Enrollment Visit, the Baseline Visit, the Randomization Visit, and the Final Evaluation Visit. Time courses of individual parameters were captured via values for each visit.

Safety and tolerability endpoints

- Adverse events and adverse events at least possibly related to the IMP.
- Vital signs (systolic and diastolic blood pressure, pulse rate, body temperature, and respiratory rate).
- Clinical laboratory values (hematology, clinical chemistry, urinalysis, and pregnancy test).
- Medication used to treat the adverse events related to the IMPs.

Endpoints of specific medical interest related to previous medication

The history of the low back pain was explored by additional questions including those related to the treatments received before the current analgesic regimen, number of regimen switches or treatment discontinuations, and functionality.

Statistical methods

Analysis of efficacy

The primary analysis was performed on the Per Protocol Set (PPS). It was also performed on the Full Analysis Set (FAS) and the modified Per Protocol Set (mPPS) as a sensitivity analysis.

The primary endpoint was analyzed using the following hypotheses:

- Null hypothesis: H0: $\mu T - \mu C > \delta$
  the TAP arm is not non-inferior to the TAP+PREG arm.
- Alternative hypothesis: H1: $\mu T - \mu C \leq \delta$
  the TAP arm is non-inferior to the TAP+PREG arm.

T = Increasing doses of tapentadol PR up to 500 mg per day.

C = Combination of tapentadol PR (300 mg per day stable) with pregabalin (300 mg per day).

δ = Non-inferiority margin.

The primary efficacy endpoint was submitted to an analysis of covariance (ANCOVA) model including treatment and center (or pooled centers if required) as factors and NRS-3 pain intensity score at Randomization as covariate. The ANCOVA provided the least square means (LSMeans) estimation as well as the treatment differences along with the relative 95% confidence interval (CI) and p-value.

The TAP arm was to be considered as non-inferior to the TAP+PREG arm if the null hypothesis could be rejected at a 1-sided 2.5% significance level using a 1-sided non-inferiority test and a non-inferiority margin of 1.2.

Descriptive summary statistics (N, mean, standard deviation [SD], median, minimum and maximum, 95% CI) are presented for continuous variables (mean tables) and the number and

percentage of subjects in each category for categorical variables (frequency tables). All the analyses were performed on the FAS. Indicative p-values are provided for special endpoints.

The descriptive comparison of all secondary endpoints was prospectively described in detail in the statistical analysis plan before unblinding.

Analysis of safety:

The analysis of safety data was performed on the Safety Set (SAF).

Clinical and statistical interpretation of the safety data were based on displays of laboratory tests, vital signs, physical examination, and adverse event data.

Sample size determination

Based on results from earlier trials with tapentadol PR, a SD of 3 for the change in pain intensity score was assumed. The non-inferiority margin δ was set to 1.2. Based on these assumptions, a sample size of 100 subjects per group was needed to reject the null hypothesis with a power of 80% using a 1-sided non-inferiority test with a significance level of 2.5%.

The primary analysis was performed on the PPS. Assuming that 70% of the subjects were available for the PPS, at least 143 subjects per treatment arm were required.

Summary of results

Subject disposition

Overall, 622 subjects were screened and signed the informed consent form. Of the screened subjects, 133 were screen failures, and 489 subjects were enrolled, 445 of them were entered and included in the SAF, and 436 in the FAS. Of the 445 subjects entered, 73 discontinued the trial prior to being randomized or allocated to the Open-Label Continuation Arm.

A total of 313 subjects in the FAS were randomized to treatment after the Open-Label Titration Period, 154 with TAP and 159 with TAP+PREG, while 59 were assigned to the Open-Label Continuation Arm.

Of the 154 subjects allocated to treatment with TAP, 139 were included in the PPS while of the159 subjects allocated to TAP+PREG, 149 were included in the PPS.

A total of 37 subjects entered the Open-label Pick-Up Arm, 19 from the group treated with TAP, and 18 from the group treated with TAP+PREG.

Demographics

Among the 445 subjects of the SAF, 183 (41.1%) were male, and 262 (58.9%) female. The mean (SD) age was 57.9 (11.30) years, ranging from 21 years to 85 years. Most of the subjects were White (441, 99.1%), 2 (0.4%) Asian and 2 (0.4%) were classified as belonging to other race. The mean (SD) height was 168.2 (9.97) cm, ranging from 135 cm to 198 cm. The mean (SD) weight was 83.61 (17.542) kg (48.2 kg to 140.2 kg). The mean (SD) body mass index was 29.57 (5.616) kg/m^2 (18.6 to 52.1 kg/m^2). The configuration of demographic characteristics was similar for the other sets analyzed.

There were no clinically relevant baseline differences between the trial arms in the demographic characteristics.

The mean (SD) age for the subjects in the Open-Label Continuation Arm was 59.2 (9.35) years, for those treated with tapentadol 58.4 (10.84) years and for those treated with the combination of tapentadol and pregabalin 55.8 (11.75) years. The subjects treated with the combination of tapentadol and pregabalin had a mean (SD) height of 169.52 (10.506) cm, those treated with tapentadol 167.84 (9.456) cm and those in the Open-Label Continuation Arm 166.3 (10.17) cm. The mean (SD) weight for the subjects treated with the combination of tapentadol and pregabalin was 85.38 (18.499) kg, for those in the Open-Label Continuation Arm 83.76 (16.74) kg and for those treated with tapentadol 81.6 (16.809) kg. The mean (SD) body mass index for the subjects in the Open-Label Continuation Arm was 30.39 (5.171) kg/m², for those treated with the combination of tapentadol and pregabalin 29.62 (5.580) kg/m² and for those treated with tapentadol 28.98 (5.616) kg/m².

The mean (SD) baseline NRS-3 pain intensity score for the overall low back pain was 8.5 (1.01) for the subjects treated with tapentadol and 8.4 (1.03) for the subjects treated with the combination of tapentadol and pregabalin.

All 313 randomized subjects (154 treated with TAP and 159 treated with TAP+PREG) were included in the SAF for the Double-Blind Comparative Arms. Of them, 309 (98.7%) were included in the FAS for the Double-Blind Comparative Arms, 241 (77%) in the painDETECT Positive Subset, 58 (18.5%) in the painDETECT Unclear Subset, and 216 (69%) in the Lumbar Radiculopathy Subset (a subset of the painDETECT Positive Subset).

Of the 154 subjects treated with TAP, 152 (98.7%) were included in the FAS for the Double-Blind Comparative Arms, 115 (74.7%) in the painDETECT Positive Subset, 29 (18.8%) in the painDETECT Unclear Subset, and 97 (63%) in the Lumbar Radiculopathy Subset.

Of the 159 subjects treated with TAP+PREG, 157 (98.7%) were included in the FAS for the Double-Blind Comparative Arms, 126 (79.2%) in the painDETECT Positive Subset, 29 (18.2%) in the painDETECT Unclear Subset, and 119 (74.8%) in the Lumbar Radiculopathy Subset.

In the PPS, the mean (SD) duration of low back pain was 9.0 (10.46) years for the subjects of the TAP arm and 8.6 (9.52) years for the subjects of the TAP+PREG arm.

The median (Q1;Q3) time to the first visit to a physician because of this pain was 0.9 (0.2;6.0) months for the subjects of the TAP arm, and 0.5 (0.2;3.5) months for the subjects of the TAP+PREG arm.

The subjects of the TAP arm visited a mean (SD) of 4.6 (7.25) doctors, while the subjects of the TAP+PREG arm visited a mean (SD) of 4.2 (3.65) doctors. The mean (SD) number of consultations within 3 months was numerically similar in subjects of both arms (3.4 [2.98] and 3.5 [3.45]), with a mean (SD) of 1.3 (1.98) and 1.2 (1.67) unplanned visits respectively.

Ninety-four subjects in the PPS had a history of hospitalization, 45 (32.4%) of the TAP arm and 49 (32.9%) of the TAP+PREG arm.

For the SAF, and the Open-Label Continuation Arm, the mean (SD) number of hospitalizations was 2.6 (2.60), and 2.3 (2.31), the mean (SD) number of hospitalizations due to lack of efficacy/unbearable pain 2.1 (2.06), and 2.0 (2.14), and due to the side effects of previous treatment 0.1 (0.58), and 0.1 (0.35), the mean (SD) number of analgesic regimens since the pain started 4.6 (4.03), and 3.5 (2.10), the number (%) of subjects not currently working 332 (74.6%), and 46 (78.0%), the mean (SD) number of times per year of being off work due to pain since the pain

started 3.1 (5.87), and 1.6 (1.80), and the mean (SD) number of months off work 2.4 (3.63), and 2.2 (2.18).

Efficacy/Effectiveness

Efficacy and quality of life endpoints for the Double-Blind Comparative Arms

Primary endpoint

The primary efficacy analysis showed a reduction of the average pain intensity elicited by both TAP and TAP+PREG in subjects with severe chronic low back pain with a neuropathic pain component. The analysis of last observation carried forward (LOCF) imputed data in the PPS demonstrated that the reduction in pain intensity on the 11-point NRS-3 pain intensity score from the Randomization Visit to the Final Evaluation Visit was comparable in the TAP arm (mean [SD] change: -1.6 [2.52]) and in the TAP+PREG arm (mean change: -1.7 [2.48]).

The ANCOVA model analysis showed that the reduction in the pain intensity score from the Randomization Visit to the Final Evaluation was comparable between TAP and TAP+PREG (LSMeans [SEM] = -0.066 [0.254]). Non-inferiority of TAP compared with TAP+PREG can be established because the upper limit of the 2-sided 95% CI (-0.57;0.43) for the LSMeans for the treatment difference was not greater than the predefined 1.2.

Secondary endpoints

During the Open-Label Titration Period, all the secondary endpoints showed significant improvements from Baseline to the Randomization Visit.

The secondary analysis of the primary endpoint and the analyses of efficacy/effectiveness and QoL endpoints with the use of LOCF imputation method supported the non-inferiority of the treatment arms in the FAS for the Double-Blind Comparative Arms and the mPPS, as well as in the painDETECT positive, and painDETECT Unclear Subsets. The analysis on observed values confirmed the robustness of the results obtained with LOCF imputed data.

<u>Pain-related endpoints</u>

For overall low back pain, pain radiating towards or into the leg and recalled worst pain during the last 24 h during the Open-Label Titration Period, the mean (SD) change from Baseline of the NRS-3 pain intensity score declined statistically significantly until the Randomization Visit.

For the Double-Blind Comparative Arms, pain intensity scores changes from the Baseline Visit to the Randomization Visit and from the Randomization Visit to the Final Evaluation Visit were similar between both treatment arms for overall low back pain, for pain radiating towards or into the leg and for recalled worst pain during the last 24 h, showing that the treatment benefits started already during the Titration Period.

The mean (SD) change in overall low back pain intensity scores from the Randomization Visit to the Final Evaluation Visit for the FAS for the Double-Blind Comparative Arms confirmed the similarity between the groups obtained for the primary endpoint with the PPS. The mean (SD) change in NRS-3 pain intensity scores from the Randomization Visit to the Final Evaluation Visit for the FAS for the Double-Blind Comparative Arms was -1.6 (2.47) for TAP, and -1.7 (2.47) for TAP+PREG.

For the overall NRS-3 pain intensity score, non-inferiority of TAP compared with TAP+PREG, as observed for the primary endpoint on the PPS, was confirmed by the secondary analysis in the FAS for the Double-Blind Comparative Arms (the upper limit of the 95% CI for the LSMeans for the treatment difference was not greater than 1.2: [-0.50;0.45]).

The mean (SD) change of the overall NRS-3 pain intensity score declined at all visits from Baseline and from Randomization to the Final Evaluation Visit in both treatment arms.

Non-inferiority of TAP monotherapy compared with TAP+PREG was also observed for pain radiating towards or into the leg: -1.5 (2.61) for the TAP arm and -1.9 (2.60) for the TAP+PREG arm (95% confidence interval = [-0.27;0.75]) considering a non-inferiority margin of 1.2, with decline at all visits from Baseline and from Randomization to the Final Evaluation Visit.

Also, the mean (SD) change in NRS-3 recalled worst pain intensity scores during the last 24 h decreased statistically significantly from the Randomization Visit to the Final Evaluation Visit and was similar in both groups: -1.7 (2.67) for TAP, and -1.8 (2.58) for TAP+PREG.

For the subjects of the Open-Label Pick-Up Arm, the mean (SD) NRS-3 pain intensity scores at the Final Evaluation Visit were generally non-statistically significantly different from Pick-Up Baseline.

Neuropathic pain-related endpoints

During the Open-Label Titration Period, the mean (SD) final scores for painDETECT at Randomization were reduced significantly compared with Baseline.

For the Double-Blind Comparative Arms, the treatment effects had an earlier onset in TAP+PREG, but were of comparable magnitude at the Final Examination.

The mean painDETECT final scores (the sum of the 7 sensory items plus the item describing the course of the pain plus the item on the presence of the radiating pain) decreased from Randomization to the Final Evaluation Visit in the subjects of both groups. The mean final scores, and thus the likelihood of detecting a neuropathic pain component of low back pain decreased over time from Randomization to the Final Evaluation Visit in the subjects of both groups with a mean (SD) change of -6.0 (8.99) for the TAP arm, and -5.9 (7.22) for the TAP+PREG arm.

The paired t-tests indicated that the changes from Baseline and from Randomization in final scores were statistically significantly lower in both groups at the Final Evaluation Visit. From the ANCOVA model analysis, no differences could be detected between treatment groups. In subjects scoring painDETECT positive and subjects scoring painDETECT unclear, the changes from Baseline and from Randomization were comparable.

In the Open-Label Pick-Up Arm, most of the subjects had painDETECT scores categorized as negative or unclear at the Final Evaluation Visit.

The monotherapy with TAP and the treatment with TAP/PREG had a comparable impact on effectiveness parameters, including typical symptoms of neuropathic pain, making it a viable option also for neuropathic pain-related symptoms.

Quality of life endpoints

From the time of the Titration Period, the subjects showed evident improvements in the QoL parameters.

Treatment with increasing doses of tapentadol PR alone or in combination with pregabalin elicited considerable improvement in the QoL of the subjects in this trial.

In general, the subjects were satisfied with the treatments received, the CGIC and PGIC reported after the treatments were very positive, the quality of sleep improved, as did the SF-12, the EQ-5D, and the HADS scores.

The number of subjects whose satisfaction with treatment assessment score was poor declined over time from Baseline to the Final Evaluation Visit, while the number of subjects whose assessment score was fair, good or very good increased. At the Final Evaluation Visit, the number of subjects (%) by assessment score was poor for 3 (2.2%) subjects in the TAP arm, and 6 (4%) subjects in the TAP+PREG arm, fair for 32 (23%) and 28 (18.8%) subjects, and good for 43 (30.9%) and 43 (28.9%) subjects in both groups. The number of subjects with assessment scores very good increased to 32 (23%) and 43 (28.9%). Assessments of excellent also increased to 21 (15.1%) and 23 (15.4%) subjects respectively.

The PGIC rating improved in both groups from Baseline through the Final Evaluation Visit. At the Final Evaluation Visit, the number of subjects (%) in the PPS who reported their impression of change as very much improved was 27 (19.4%) for the TAP arm and 31 (20.8%) for the subjects treated with TAP+PREG. The rating was much improved for 40 (28.8%) and 64 (43%) respectively, while it was minimally improved for 47 (33.8%) and 27 (18.1%) correspondingly. No change was reported by 9 (6.5%) and 10 (6.7%) subjects, while the rating of much worse was given by 4 (2.9%) and 5 (3.4%) subjects in each group. Only 1 (0.7%) subject treated with TAP+PREG provided a rating of very much worse. The 2-sided p-value for the Cochran Mantel Haenszel test was 0.5357, indicating that no significant difference could be detected between the groups.

The CGIC rating improved in both groups from Baseline through the Final Evaluation Visit. At the Final Evaluation Visit, the clinicians evaluated the overall condition of their subjects in the PPS as very much improved for 25 (18%) subjects in the TAP arm and 29 (19.5%) subjects treated with TAP+PREG. The rating was much improved for 51 (36.7%) and 77 (51.7%) respectively, while it was minimally improved for 41 (29.5%) and 18 (12.1%) correspondingly. No change was reported for 7 (5%) and 10 (6.7%) subjects, while the rating of much worse was given for 5 (3.6%) and 5 (3.4%) subjects in each group. Two (1.3%) subjects treated with TAP+PREG received a rating of very much worse. The 2-sided p-value for the Cochran Mantel Haenszel test was 0.5421, indicating that no significant difference could be detected between the groups.

As to the SQ items, latency, number of awakenings and time slept, the change from Baseline and from Randomization, as well as the overall quality of sleep, improved significantly over time for both treatment arms. At the Final Evaluation Visit, the mean (SD) change from Baseline in latency was -0.3 (2.30) h for the TAP arm, and -0.3 (2.10) h for the TAP+PREG arm with a mean (SD) change from randomization of 0.2 (1.88) h and -0.2 (2.04) h. The mean number of awakenings decreased over time. At the Final Evaluation Visit, the mean (SD) change from Baseline was -1.4 (2.57) and -2.5 (3.11) and the mean (SD) change from randomization was -0.2 (2.01) and -0.8 (1.78). The mean time that subjects slept during the night increased significantly over time. At the Final Evaluation Visit, the mean (SD) change from Baseline was 1.2 (1.89) h and 1.6 (1.84) h and the mean (SD) change from randomization was 0.3 (1.71) h and 0.3 (1.70) h. The overall quality of sleep improved over time. At the Final Evaluation Visit, the shift from Randomization was rated as improvement by 39 (28.1%) and 58 (38.9%) subjects, as no change by 63 (45.3%) and 59 (39.6%) subjects, and as worsening by 21 (15.1%) and 20 (13.4%) subjects.

The mean HADS anxiety and depression scores decreased at every point of assessment from Baseline to the Final Evaluation Visit. For the LOCF imputed data, the mean (SD) anxiety score of the HADS at Baseline was 7.7 (4.52) for the subjects allocated to the TAP arm and 9.0 (5.15) for the subjects allocated to TAP+PREG. At Randomization, the mean (SD) anxiety score was 5.8 (3.77) and 7.1 (4.39). The change from Baseline for the anxiety score was -1.9 (2.91) and -1.9 (3.55) respectively ($p<0.0001$). At the Final Evaluation Visit, the mean (SD) anxiety score of the HADS was 5.8 (4.49) for the TAP arm and 5.8 (4.42) for the subjects treated with TAP+PREG, the mean change from Baseline in the anxiety score was -2.2 (3.70) and -3.1 (4.28) and the mean (SD) change from Randomization was -0.3 (2.93) and -1.2 (3.38).

The mean depression score also decreased at every point of assessment from Baseline to the Final Evaluation Visit. For the LOCF imputed data, the mean (SD) depression score of the HADS at Baseline was 7.6 (4.66) for the TAP arm and 8.6 (4.81) for the subjects treated with TAP+PREG. At Randomization, the mean (SD) depression score was 6.0 (3.96) and 6.8 (4.24). The change from Baseline for the depression score was -1.6 (2.66) and -1.8 (3.19) respectively ($p<0.0001$). At the Final Evaluation Visit, the mean (SD) depression score of the HADS was 5.9 (4.70) for the TAP arm and 5.3 (4.05) for the subjects treated with TAP+PREG, the mean change from Baseline in the depression score was -2.0 (3.56) and -3.1 (3.99) and the mean (SD) change from Randomization was -0.4 (3.06) and -1.3 (2.94).

For most of the SF-12 health domain scales, there were statistically significant changes in the mean scores from Baseline to Randomization and to the Final Evaluation Visit, indicating an increase in the subjects' general health status.

The mean EQ-5D index and visual analogue scale (VAS) scores increased over time up to the Final Evaluation Visit and remained stable thereafter, statistically different from Baseline at all the time points of evaluation. The mean (SD) index scores at Baseline were 0.29 (0.306) for the TAP arm, and 0.18 (0.316) in the TAP+PREG arm. At Randomization, the mean (SD) change from Baseline was 0.26 (0.322) and 0.34 (0.340). At the Final Evaluation Visit, the mean (SD) change from Baseline was 0.34 (0.358) and 0.43 (0.386), and the mean (SD) change from Randomization was 0.09 (0.317) and 0.09 (0.254).

The mean (SD) VAS scores at Baseline were 39.1 (22.10) for the TAP arm, and 37.1 (22.96) in the TAP+PREG arm. At Randomization, the mean (SD) change from Baseline was 14.3 (18.62) and 14.3 (24.76). At the Final Evaluation Visit, the mean (SD) change from Baseline was 22.6 (33.08) and 27.9 (30.54), and the mean (SD) change from Randomization was 8.4 (27.93) and 13.5 (25.23).

A similar trend in the QoL endpoints was observed in the Open-Label Pick-Up Arm.

Efficacy and quality of life for the Open-Label Continuation Arm

Pain-related endpoints

For overall low back pain, pain radiating towards or into the leg and recalled worst pain during the last 24 h during the Open-Label Continuation Arm, the mean (SD) change from Baseline of the NRS-3 pain intensity score declined statistically significantly at the Randomization Visit. Statistically significant reductions in pain intensity scores were also observed from the Baseline Visit to the Final Evaluation Visit. The changes from the Randomization Visit to the Final Evaluation Visit were generally not statistically significant.

Neuropathic pain-related endpoints

At Randomization, the mean (SD) final scores for painDETECT were reduced significantly to 11.0 (5.92; paired t-test p-value <0.0001), with a change from Baseline of -12.3 (7.20). At the Final Evaluation Visit, the mean (SD) final score for painDETECT was reduced significantly to 8.9 (5.38; paired t-test p-value <0.05), with a change from Baseline of -15.0 (7.03), and a change from Randomization of -1.8 (5.25).

The NPSI total score and subscores, the duration of spontaneous pain, and the number of pain attacks during the past 24 h were significantly improved over time during the trial. The mean (SD) total score at Baseline was 63.3 (15.62) and decreased at Randomization to 19.8 (13.31), with a statistically significant change from Baseline of -43.5 (17.84). At the Final Evaluation Visit, the change from Baseline was -48.8 (19.00) and the change from Randomization -4.7 (10.67).

Quality of life endpoints

In general, the QoL endpoints during the Open-Label Continuation Arm improved over time from the Baseline Visit to the Final Evaluation Visit.

Safety and tolerability

Overall, 445 subjects in the Open-Label Titration Arm were exposed to tapentadol PR and entered the SAF. The mean (SD) exposure time was 18.6 (5.10) days in the Titration Period that had a planned duration of up to 21 days.

A total of 154 subjects in the TAP arm were exposed to tapentadol PR (mean [SD] exposure time: 51.3 [21.69] days), and 159 subjects in the TAP+PREG arm were exposed to the IMPs (mean [SD] exposure time: 53.4 [20.42] days) during the Comparative Period that had a planned duration of up to 55 days. A total of 37 subjects in the Open-Label Pick-Up Arm, and 59 subjects in the Open-Label Continuation Arm were exposed to tapentadol PR.

Non-TEAEs did not provide any indication of their relationship with trial procedures, except for 2 occurrences of drug withdrawal syndrome. One subject died and 1 subject discontinued due to middle insomnia prior to the start of the treatment.

Overall 316 (71.0%) of the 445 subjects in the SAF reported 1264 TEAEs during the whole trial.

A total of 37 subjects entered the Open-label Pick-Up Arm due to TEAEs, 19 from the group treated with tapentadol PR, and 18 from the group treated with the combination of tapentadol PR and pregabalin.

In total, 15 (3.4%) subjects reported 19 serious TEAEs during the trial and 79 (17.8%) subjects reported 194 TEAEs that led to their discontinuation from the trial. Of the 19 serious TEAEs, 4 occurred during the Open-Label Titration Period, 11 in the Comparative Period (6 in the TAP arm, and 5 in the TAP+PREG arm), 3 in the Open-Label Pick-Up Arm, and 1 in the Open-Label Continuation Arm. There was 1 death in the trial due to TEAEs. Subject [redacted] (treated with TAP+PREG during the Double-Blind Comparative Period and later allocated to the Open-Label Pick-Up Arm) died because of pulmonary embolism, and cardiac arrest unlikely related to the IMP.

Treatment emergent adverse events leading to discontinuation emerged in 52 (11.7%) subjects (131 TEAEs) during the Open-Label Titration Period, in 12 (7.8%) subjects (20 TEAEs) during treatment in the TAP arm, in 13 (8.2%) subjects (27 TEAEs) during treatment in the TAP+PREG arm, in 5 (13.5%) subjects (8 TEAEs) during treatment in the Open-Label Pick-Up Arm, and

3 (5.1%) subjects (8 TEAEs) during treatment in the Open-Label Continuation Arm. However not all subjects discontinued in the same treatment arm/period during which the respective TEAEs (reason for discontinuation) emerged and 6 subjects reported at least 2 TEAEs leading to discontinuation, which emerged in different treatment arms or periods.

In total, 41 subjects discontinued the trial due to TEAEs during the Open-Label Titration Period, 12 subjects during treatment in the TAP arm and TAP+PREG arm each, 10 subjects during treatment in the Open-Label Pick-Up Arm and 4 subjects during treatment in the Open-Label Continuation Arm.

The TEAEs that affected at least 5% of the subjects were dizziness, nausea, somnolence, headache, fatigue, dry mouth, hyperhidrosis, constipation, and vomiting.

During the Open-Label Titration Period, 227 (51.0%) subjects reported 592 TEAEs. The most frequent TEAEs reported concerned mainly gastrointestinal disorders 133 (29.9%) subjects with 183 TEAEs, and nervous system disorders 116 (26.1%) subjects with 162 TEAEs.

During the Comparative Period, 98 (63.6%) subjects in the TAP arm reported 270 TEAEs and 103 (64.8%) subjects in TAP+PREG group reported 309 TEAEs.

For the subjects treated with TAP, the TEAEs that affected at least 5% of the subjects were hyperhidrosis 18 (11.7%) subjects with 18 TEAEs, dizziness 17 (11.0%) subjects with 17 TEAEs, nausea 16 (10.4%) subjects with 20 TEAEs, somnolence 13 (8.4%) subjects with 13 TEAEs, fatigue 13 (8.4%) subjects with 13 TEAEs, constipation 11 (7.1%) subjects with 13 TEAEs, headache 10 (6.5%) subjects with 16 TEAEs, and vomiting 9 (5.8%) subjects with 9 TEAEs.

For the subjects treated with TAP+PREG, The TEAEs that affected at least 5% of the subjects were dizziness 28 (17.6%) subjects with 35 TEAEs, somnolence 19 (11.9%) subjects with 20 TEAEs, fatigue 16 (10.1%) subjects with 17 TEAEs, nausea 15 (9.4%) subjects with 15 TEAEs, headache 13 (8.2%) subjects with 22 TEAEs, hyperhidrosis 10 (6.3%) subjects with 11 TEAEs, and constipation 8 (5.0%) subjects with 8 TEAEs.

No significant differences were observed for the system organ classes between the 2 treatment arms. There was also no significant difference for hyperhidrosis between those arms. There was a significant difference for the composite parameter dizziness and somnolence, the 2 most frequent newly occurring TEAEs in the double blind arms of the comparative period.

The worst intensity of the related TEAEs during the whole trial in the SAF was assessed as mild for 616 (67.2%) TEAEs, moderate for 264 (28.8%) TEAEs and severe for 36 (3.9%) TEAEs. Of the 916 related TEAEs reported during the whole trial, 565 (61.7%) were considered possibly related to the IMP, 278 (30.3%) as probable/likely related to the IMP, and 73 (8.0%) as certainly related to the IMP. In the TAP arm, the worst intensity of the related TEAEs during the Comparative Period was assessed as mild for 119 (64.0%) TEAEs, moderate for 63 (33.9%) TEAEs and severe for 4 (2.2%) TEAEs. In the TAP+PREG arm, the worst intensity of the related TEAEs during the Comparative Period was assessed as mild for 120 (59.1%) TEAEs, moderate for 66 (32.5%) TEAEs and severe for 17 (8.4%) TEAEs.

The TEAEs that affected at least 5% of the subjects in the Open-Label Continuation Arm were constipation 3 (5.1%) subjects with 3 TEAEs, nausea 3 (5.1%) subjects with 3 TEAEs, nasopharyngitis 3 (5.1%) subjects with 3 TEAEs, and somnolence 3 (5.1%) subjects with 3 TEAEs.

Although with frequencies lower than 5%, dizziness, fatigue, hyperhidrosis, headache, vomiting and diarrhea were medically significant TEAEs.

Only 1 preferred term affected at least 5% of the subjects during the Open-Label Pick-Up Arm, decreased appetite with 2 (5.4%) subjects (both from the TAP+PREG arm) who reported 2 TEAEs. There were infrequent changes in clinical laboratory parameters, and vital signs, but no consistent change could be attributed specifically to the administration of the IMPs.

The safety profile was consistent with the known safety profile for tapentadol and pregabalin. No new adverse drug reaction could be identified. The safety profile of tapentadol remained favorable up to the maximum daily doses. When combined with pregabalin, particularly CNS effects (dizziness/somnolence) increased in a clinically relevant way. Compared with historical combination trials with opioids and anticonvulsants, the tolerability profile can be judged overall as positive also for the TAP+PREG arm.

Conclusion

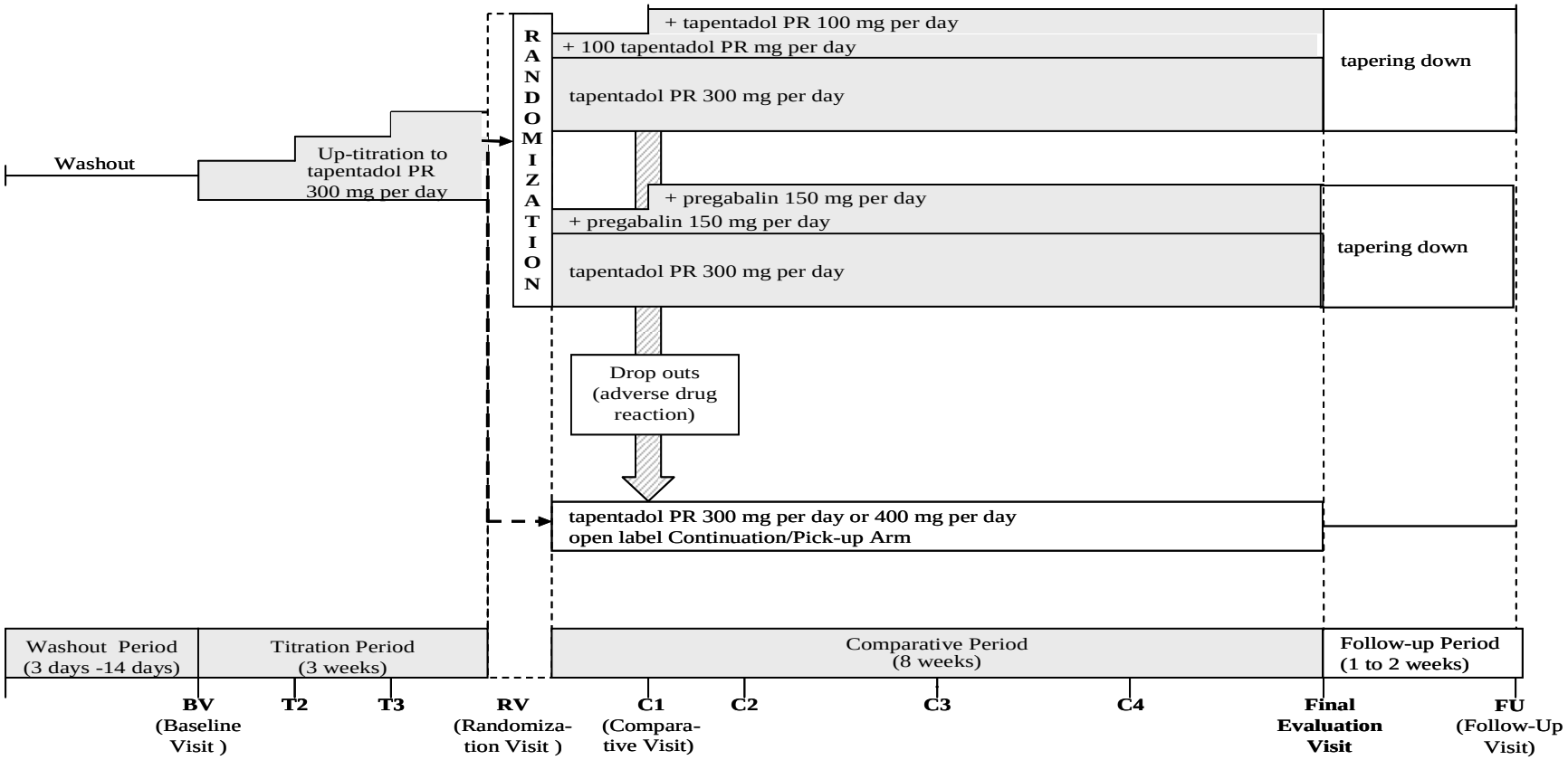
- Similar reductions in average pain intensity (NRS-3) were observed from randomization to final evaluation with tapentadol PR 500 mg, compared with tapentadol PR 300 mg plus pregabalin 300 mg.
  - The primary endpoint was reached, showing the non-inferiority of tapentadol PR monotherapy compared with the combination therapy with moderate doses of tapentadol PR plus pregabalin.
  - For subjects with severe low back pain with a neuropathic pain responding partially to doses of tapentadol PR up to 300 mg/day, better effectiveness can be achieved by increasing the dose up to 500 mg/day.
- Both double-blind treatment regimens were associated with clinically relevant reductions in radiating pain and other neuropathy-related sensory symptoms (as measured with painDETECT and NPSI questionnaires).
- Tapentadol PR was generally well tolerated.
  - During the Titration Period, only 11.7% of the subjects discontinued from the trial due to TEAEs.
  - The rates of trial discontinuation due to TEAEs were low (<10%) in both treatment arms during the Comparative Period.
  - In the double-blind comparative period, there was a higher incidence of newly occurring CNS-related TEAEs with tapentadol PR 300 mg plus pregabalin 300 mg when compared to tapentadol PR 500 mg monotherapy. This was mainly due to a significantly larger incidence of the composite TEAE dizziness/somnolence in the combination arm (16.88% TAP versus 27.04% TAP+PREG, p-value = 0.0302).
  - While the percentage of related TEAEs of mild and moderate intensity was comparable between the double blind arms (TAP 119 [64.0%] mild TEAEs and 63 [33.9%] moderate TEAEs; TAP+PREG: 120 [59.1%] mild TEAEs and 66 [32.5%] moderate TEAEs). Tapentadol PR was associated with less severe TEAEs than the combination therapy (2.2% versus 8.4%).

- Overall, tapentadol PR monotherapy is effective for the treatment of patients with severe low back pain with a neuropathic pain component, is well tolerated up to a dose of 500 mg/day, and reflects a viable treatment option in this indication.
- The risk-benefit ratio of tapentadol remains unchanged positive.
- The side effect profile when combining tapentadol PR with pregabalin remains acceptable and more positive compared with historical data from combination trials of strong opioids and anticonvulsants.
- A subpopulation of subjects with low back pain with a neuropathic pain component that was potentially less chronified and more prone to respond (faster) to a restoration of descending inhibition responded very well to a dose of tapentadol PR of 300 mg/day; further exploration into the characteristics of this low-dose responder group is needed to elucidate possible underlying factors associated with a very positive treatment response.

Publications based on this trial

Baron R, Kern K-U, Buunen M, Steigerwald I. Impact of tapentadol prolonged release (PR) versus a combination of tapentadol PR and pregabalin on the neuropathic component of severe, chronic low back pain. Poster No. 289, presented at the American Society of Regional Anesthesia and Pain Medicine, Miami, Florida. USA, 15-18 Nov 2012.

Steigerwald I, Kern U, Buunen M, Baron R. Effectiveness of tapentadol prolonged release (PR) versus a combination of tapentadol PR and pregabalin for managing severe, chronic low back pain with a neuropathic component. Poster No. 288, presented at the American Society of Regional Anesthesia and Pain Medicine, Miami, Florida. USA, 15-18 Nov 2012.



Flow diagram of the trial

ICTR SYNOPSIS SUPPLEMENT

KF5503/58

Original ICTR issue date:	26 Mar 2013	**DMS version:**	2.0
ICTR synopsis supplement date:	09 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 no amendments to the protocol.

3 INFORMATION REGARDING CLINICAL HOLD OR EARLY TERMINATION

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

4 NAMES AND ADDRESSES OF PRINCIPAL INVESTIGATORS

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

Site number	Investigator	Site address
43 501	(Name not given, since no consent given)	1090 Wien, Austria
43 503	(Name not given, since no consent given)	3541 Senftenberg, Austria
43 504	(Name not given, since no consent given)	1100 Wien, Austria
43 505	(Name not given, since no consent given)	1090 Wien, Austria
43 506	(Name not given, since no consent given)	9020 Klagenfurt, Austria
32 601	(Name not given, since no consent given)	3212 Pellenberg, Belgium
32 602	(Name not given, since no consent given)	3600 Genk, Belgium
32 603	(Name not given, since no consent given)	6534 Gozee, Belgium
32 604	(Name not given, since no consent given)	3945 Ham, Belgium
32 605	(Name not given, since no consent given)	7370 Dour, Belgium
45 701	(Name not given, since no consent given)	2600 Glostrup, Denmark
45 702	(Name not given, since no consent given)	1100 København, Denmark
45 703	(Name not given, since no consent given)	4100 Ringsted, Denmark
45 704	(Name not given, since no consent given)	2000 Frederiksberg, Denmark
49 101	(Name not given, since no consent given)	24105 Kiel, Germany
49 103	(Name not given, since no consent given)	22767 Hamburg, Germany
49 104	(Name not given, since no consent given)	65189 Wiesbaden, Germany
49 105	(Name not given, since no consent given)	51069 Köln, Germany
49 106	(Name not given, since no consent given)	24768 Rendsburg, Germany

Site number	Investigator	Site address
49 108	(Name not given, since no consent given)	74821 Mosbach, Germany
49 111 + 119	(Name not given, since no consent given)	04564 Böhlen, Germany
49 112 + 120	(Name not given, since no consent given)	26655 Westerede, Germany
49 113 + 121	(Name not given, since no consent given)	04103 Leipzig, Germany
49 114	(Name not given, since no consent given)	24106 Kiel, Germany
49 115 + 123	(Name not given, since no consent given)	03050 Cottbus, Germany
49 116 + 122	(Name not given, since no consent given)	50924 Köln, Germany
49 118	(Name not given, since no consent given)	10787 Berlin, Germany
31 801	(Name not given, since no consent given)	3361 XV Sliedrecht, Netherlands
31 803	(Name not given, since no consent given)	1081 HV Amsterdam, Netherlands
31 804	(Name not given, since no consent given)	5623 EJ Eindhoven, Netherlands
31 805	(Name not given, since no consent given)	7513 ER Enschede, Netherlands
48 301	(Name not given, since no consent given)	02-256 Warsaw, Poland
48 302	(Name not given, since no consent given)	01-192 Warsaw, Poland
48 303	(Name not given, since no consent given)	40-748 Katowice, Poland
48 304	(Name not given, since no consent given)	61-289 Poznan, Poland
48 305	(Name not given, since no consent given)	50-349 Wroclaw, Poland
48 306	(Name not given, since no consent given)	07-300 Ostrów Mazowiecka, Poland
48 307	(Name not given, since no consent given)	20-093 Lublin, Poland
48 308	(Name not given, since no consent given)	30-510 Krakow, Poland
48 309	(Name not given, since no consent given)	85-796 Bydgoszcz, Poland
48 310	(Name not given, since no consent given)	85-825 Grodzisk Mazowiecki, Poland
34 901	(Name not given, since no consent given)	08916 Badalona, Spain
34 902	(Name not given, since no consent given)	08540 Centelles, Spain
34 903	(Name not given, since no consent given)	33009 Oviedo, Spain
34 904	(Name not given, since no consent given)	15006 A Coruna, Spain
34 905	(Name not given, since no consent given)	08041 Barcelona, Spain
34 909	(Name not given, since no consent given)	28046 Madrid, Spain
34 910	(Name not given, since no consent given)	28005 Madrid, Spain
34 911	(Name not given, since no consent given)	46009 Valencia, Spain

5 PUBLICATION OF TRIAL RESULTS IN MEDICAL JOURNALS

The results of the KF5503/58 clinical trial have been published in the following medical journals:

Baron R, Kern U, Müller M, Dubois C, Falke D, Steigerwald I. Effectiveness and tolerability of a moderate dose of tapentadol prolonged release for managing severe, chronic low back pain with a neuropathic component: an open-label continuation arm of a randomized Phase 3b study. Pain Practice 2015; 15 (5): 471-86.

Baron R, Martin-Mola E, Müller M, Dubois C, Falke D, Steigerwald I. Effectiveness and safety of tapentadol prolonged release (PR) versus a combination of tapentadol PR and pregabalin for the management of severe, chronic low back pain with a neuropathic component: a randomized, double-blind, Phase 3b study. Pain Practice 2015; 15 (5): 455-70.

Baron R, Schwittay A, Falke D, Samper D, Steigerwald. Results of Patient and Clinician Global Impressions of Change with tapentadol prolonged release (PR) versus tapentadol PR/pregabalin combination therapy in patients with severe, chronic low back pain with a neuropathic component. Poster presented at the British Pain Society (BPS) 2013 Annual Scientific Meeting, April 16-19, 2013, Bournemouth, England.

Samper D, Schwittay A, Falke D, Baron R, Steigerwald I. Functional health and well-being outcomes with tapentadol prolonged release (PR) versus tapentadol PR/pregabalin combination therapy in patients with severe, chronic low back pain with a neuropathic component. Poster presented at the British Pain Society (BPS) 2013 Annual Scientific Meeting, April 16-19, 2013, Bournemouth, England.