2 SYNOPSIS

Trial number	KF5503/53
Title of trial	A multicenter, open-label trial to assess cognitive and psychomotor performance as surrogate parameters for driving ability under stable long-term treatment with tapentadol hydrochloride prolonged-release tablets in subjects with chronic low back pain or osteoarthritis of the knee.
Trial design	Non-randomized, multicenter, open-label, multiple administration Phase IIIb trial in a proposed total number of 30 subjects.
Development phase	Phase IIIb
EudraCT number.	2009-015397-35
Publication number	312937
Indication	Psychomotor performance as a surrogate parameter for driving ability in subjects with chronic low back pain or osteoarthritis of the knee
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany
Principal investigator	[redacted]
Trial site	[redacted]
Trial period	First subject enrolled: 26 Feb 2010 Last subject completed: 03 Sep 2010

Objectives

The objective of this trial was to evaluate the cognitive and psychomotor performance as measured by a validated methodology (Vienna Test System – Traffic Plus) based on a global judgment as the key outcome surrogate parameter for driving ability in subjects with chronic non-malignant pain under stable treatment with tapentadol prolonged (PR) tablets.

Investigational medicinal products (IMPs)

Tapentadol PR 50 mg to 250 mg twice daily, oral:

- Tapentadol PR 50 mg prolonged-release tablets: batch number 102M10, expiry date 03/2011.
- Tapentadol PR 100 mg prolonged-release tablets: batch number 101M10, expiry date 04/2011.

- Tapentadol PR 150 mg prolonged-release tablets: batch number 102M11, expiry date 03/2011.
- Tapentadol PR 200 mg prolonged-release tablets: batch number 102A06, expiry date 06/2012.
- Tapentadol PR 250 mg prolonged-release tablets: batch number 102L06, expiry date 09/2010.

Tapentadol IR 50 mg as required, oral:

- Tapentadol IR 50 mg film-coated tablets: batch number 104M06, expiry date 01/2011.

Treatments

Subjects were on an individually titrated (to effect and tolerability) but stable dose of tapentadol PR taken twice daily, approximately 12 hours apart. The dose range of tapentadol PR was 50 mg to 250 mg taken twice daily (maximal 30% of subjects with the lowest dose of 50 mg twice daily). The treatment could be taken independently of food intake.

In addition, tapentadol IR 50 mg could be taken on demand (at least 4 hours apart and no more than twice daily) up to a total daily dose of 500 mg of tapentadol. Tapentadol IR was not to be given to subjects who were taking tapentadol PR 250 mg twice daily (500 mg total daily dose). No additional medication was allowed for the relief of pain during this time.

No tapentadol IR dose was allowed on the day before the Test Visit, and on the Test Visit day before completion of the Vienna Test System – Traffic.

Trial population

Subjects had to be at least 18 years of age but younger than 70 years old, to have completed 1 of the previous trials KF5503/42, KF5503/43, KF5503/44, or KF5503/45 (trials of painful osteoarthritis and low back pain), and to have been on a stable dose of tapentadol PR for at least 2 weeks.

Methodology

During the Enrollment Period, subjects were evaluated for their suitability for the trial at the originating site, and arrangements were made for them to travel to the test site.

At the Test Visit, subjects were instructed and trained on the Vienna Test System – Traffic Plus.

A Final Visit was performed at the originating site.

Data collected

Efficacy related parameter

Pain intensity score on an 11-point numerical rating scale with 3 days recall (NRS-3).

Pharmacodynamics

Vienna Test System – Traffic Plus comprising:

- Global judgment of driving ability.
- Adaptive matrices test.
- Cognitrone.
- Tachistoskopic traffic conception test.
- Reaction test.

- Determination test.
- Peripheral perception test.
- Vienna Risk Willingness Test Traffic.
- Two-hand coordination test.
- Vigilance.
- Visual pursuit test.

Safety

Adverse events (recording throughout the trial, specific evaluation at each visit), physical examination, and vital signs (systolic and diastolic blood pressure, pulse, and respiratory rate).

Statistical methods

Sample size

A sample size of approximately 30 subjects is generally used for exploratory trials on driving ability. A total of 30 subjects were considered sufficient to descriptively explore the effect of multiple doses of tapentadol PR on cognitive and psychomotor performance as surrogate parameters for driving ability.

Pharmacodynamic and efficacy

Summary statistics were calculated for the pharmacodynamic and efficacy parameters. Analyses were performed on the Per Protocol Set.

Analyses of Vienna Test System - Traffic Plus results

The analyses was performed using the Per Protocol Set, which included all the subjects who completed the following 6 tests of the test battery “Plus” of the Vienna Test System - Traffic and had no major protocol deviations that could impact the primary outcome:

- Adaptive matrices test.
- Cognitrone.
- Tachistoskopic traffic conception test.
- Reaction test.
- Determination test.
- Peripheral perception test.

The Vienna Test System - Traffic Plus generated a global judgment of the respondent’s driving-specific ability, which was displayed using absolute and relative frequencies, based on the 6 tests.

The global judgment determined (binary classification: yes or no) whether the subject’s psychomotor performance and cognition fulfilled the criteria of driving a car safely. The subjects were allocated as follows:

The outcome of the global judgment was considered positive when 1 of the following results was observed:

- Adequate driving-related ability.
- Adequate driving-related ability (performance deficits could be compensated).

- Subjects with performance deficits that could be compensated according to predefined criteria to a limited extent were classified as “fit to drive” if scores obtained for each single test (cognitrone, tachistoskopic traffic conception test, or determination test) were greater than or equal to the pre-specified 16th percentile.

The outcome of the global judgment was considered negative when 1 of the following results was observed:

- Subjects with performance deficits that can be compensated to a limited extent were classified as “not fit to drive” if their scores obtained for at least 1 single test (cognitrone, tachistoskopic traffic conception test, or determination test) were lower to the pre-specified 16th percentile.
- Non-compensable performance deficits.
- Inadequate driving–related ability.

Unlike comparable trials with buprenorphine, fentanyl, and oxycodone, this trial did not compare subjects receiving tapentadol PR to a group of historical controls consisting of untreated, healthy subjects. As justification, the Vienna Test System - Traffic Plus has the potential for an inherent comparison to a reference population. Therefore, no comparative treatment arm was required in this trial as the test system has been validated against a standardized driving test (Risser et al. 2008), primarily predicting the result of a standardized driving test taken by a car driver, and threshold values for each test are defined as the 16th percentile of normally distributed test data from a representative age-independent sample that has been transformed into a standard normal distribution.

The endpoint criteria were assessed descriptively as follows:

- Global judgment as the key outcome surrogate parameter for driving ability.
- A binary outcome was created for each of the individual performance tests of the Vienna tests system, with a successful outcome being defined as the subject having a score that is equal to or higher than the 16th percentile of the respective test, as has been validated in a healthy subject population).
- Pain intensity score on an 11-point NRS-3 at the Enrollment Visit and the Final Visit, and on the 11-point NRS at the Test Visit.

For each of the test scores of the Vienna Test System - Traffic Plus, absolute and relative frequencies were used to display the classification of subject responses that were less than, greater than or equal to a percentile ranking of 16. These endpoints were descriptively summarized.

Analyses of safety

Safety analyses were performed using the Safety Set which includes all subjects enrolled who took at least 1 dose of tapentadol PR or tapentadol IR.

Summary statistics were calculated and all data were listed.

Summary of results

Subject disposition

The trial started on 26 Feb 2010 with the enrollment of the first subject and was completed on 03 Sep 2010 when the last subject completed the last follow-up. There were 7 sites in Germany that contributed subjects to the trial site.

A total of 38 subjects were enrolled and all were included in the trial. No subjects dropped out during the course of the trial.

Actual enrolled	Treated	Evaluated	
		Safety Set	Per Protocol Set
38	38	38	35

Demographics

There were 14 men and 24 women included in the trial. The mean (standard deviation [SD]) age was 58.0 (6.95) years, mean (SD) height was 171.7 (8.91) cm, mean (SD) weight was 93.88 (19.199) kg, and the mean (SD) body mass index was 31.96 (6.711) kg/m^2.

Efficacy related parameter

Pain scores of subjects did not notably differ between the start and end of this trial. At the Final Visit the mean (SD) pain score was 2.5 (1.62) with a mean (SD) change from the Enrollment Visit of -0.2 (1.0) on the NRS-3.

Pharmacodynamics

The global judgment of driving specific ability as assessed by the Vienna Test System – Traffic Plus classified approximately 2 thirds of subjects on tapentadol PR treatment to be fit to drive. All but the adaptive matrices test supported the results of the global judgment.

Discussion of driving ability-related outcome parameters

The key tests for the comparison of tapentadol to other compounds that have already shown non-inferiority in healthy subjects in published literature are the cognitrone test, tachistoskopic traffic conception test, determination test, vigilance test, and the 2-hand coordination test.

The percentage of subjects with an individual result >16th percentile for the cognitrone test, tachistoskopic traffic conception test, determination test, vigilance test, and the 2-hand coordination test were at least comparable to the results in a trial with transdermal buprenorphine (Dagetkin et al. 2007) and with transdermal fentanyl (Sabatowski et al. 2003). Although subjects under tapentadol performed even better in some of the parameters in these tests compared to other strong opioids, the driving ability of subjects under stable treatment with tapentadol PR is considered at least to be comparable to the driving ability of subjects under stable treatment with fentanyl or buprenorphine where the overall results showed non-inferiority of the subjects tested compared to healthy subjects.

Several variables must be considered that might have an impact on performance. These must be assessed with caution due to the exploratory nature of the analyses. Explorative analyses showed that there was a statistical (but non-significant) tendency that subjects with an intelligence quotient (IQ) of ≥85 performed better in the test system and were more fit to drive. Subjects over 58 years of age performed significantly worse in the test system and were less fit to drive. Subjects who had driven more than 9000 kilometers in the previous year tended to be classified as more fit to drive.

There was no effect of dose of tapentadol PR, current pain intensity, or level of education on the global judgment outcome.

Safety and tolerability

There were 2 non-serious treatment emergent adverse events (TEAEs) reported in 2 subjects (5.3%) which were considered to be not related to the IMP by the investigator. There were no deaths, other serious adverse events, or adverse events leading to discontinuation. Apart from a higher blood pressure and pulse rate at the Test Visit, which was not considered to be medically significant, there were no notable changes in blood pressure, pulse rate, respiratory rate, or physical examination during the trial. An analysis of laboratory parameter changes was not performed for this trial.

Conclusion

Based on the global judgment, the results of this trial indicate that subjects suffering from chronic non-malignant pain who are treated with a stable dose of tapentadol PR do not have a clinically significant impairment of psychomotor or cognitive function that would prevent them from performing complex daily activities such as driving a car. In general, apart from the adaptive matrix score, individual item scores of the Vienna Test System - Traffic Plus were in line with the global judgment.

In conclusion, the results of this trial imply that stable treatment with tapentadol PR in chronic non-malignant pain conditions does not impair driving ability. However, as a result of the individual variability of the test results, an individual assessment of subjects who are prescribed tapentadol should be taken into account in case of uncertainty for an individual subject (for example, subjects with additional risk factors).

The driving ability of subjects under stable treatment with tapentadol PR was comparable to the driving ability of subjects under treatment with fentanyl or buprenorphine where the overall results showed non-inferiority of the subjects tested compared to healthy subjects.

Overall, the safety profile of tapentadol PR in this trial was consistent with that observed in previous multiple dose trials with tapentadol PR.

Publications based on this trial

Not applicable.

ICTR SYNOPSIS SUPPLEMENT

KF5503/53

Original ICTR issue date:	24 Nov 2011	**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 02 amendments to the protocol.

The following changes were documented:

Amendment 01

The signatories of the protocol were reduced to match revised sponsor standards.

The original protocol text for 1 of the secondary endpoints was based on the English user's manual of the test system, according to which the summarization of individual test results in a global judgment of the driving ability was to be reported as a percentage. The German version of the system was used in the trial; hence the global judgment was to be reported as a binary classification according to the German user's manual of the test system which is the primary endpoint; therefore, the secondary endpoint global judgment reported as percentage was removed.

New sections were inserted to describe the assessment of the NRS and the NRS-3 for the collection of pain intensity data.

No urine drug test was planned in the originating trials KF5503/42, KF5503/43, KF5503/44, or KF5503/45 which supplied the subjects for this trial. The relevant text in the list of assessments for the Enrollment Visit was reworded and the link to the urine drug test in the preceding trials was removed.

Trial data recorded in electronic case report form was clarified. The descriptions relevant to paper case report forms were deleted. Further changes reflected that due to technical reasons, the data from the Vienna Test System-Traffic Plus would not be transferred electronically but would be typed in by the test investigator.

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

Amendment 02

Due to a re-evaluation of the group evaluation system underlying the new Vienna Test System-Traffic Plus, the originally chosen descriptive primary endpoint of the trial was inappropriate as it referred to a very small subset of the overall population able to drive. It did not allow for a statement to be made on driving ability of the trial population pretreated with tapentadol PR. Therefore, there is a scientific need to amend the trial with regard to evaluating the driving ability in this trial population.

As the originally chosen primary endpoint of the trial (subjects must achieve at least the specified cut-off score [16th percentile] in all [i.e., every single one] of the performance tests used) with tapentadol is inappropriate to differentiate subjects who are fit to drive from those who are not — as it only describes a small subset of persons passing all tests without deficiencies and an IQ>70 — the endpoint criteria was to be summarized focusing on the "global judgment".

Hence, modifications were implemented in Amendment 2 to the rationale, the objective, the endpoints, and the analysis.

Other changes made in this protocol amendment:

- The signatories of the protocol as document author and trial biostatistician were updated to reflect the current study team structure.
- Editorial modifications were included and text additions were implemented in relevant sections.

This amendment was considered substantial and was implemented after approval by the study team and the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) on 29 Jul 2011.

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
DE022	(Name not given, since no consent given)	98746 Katzhuette, Germany
DE023	(Name not given, since no consent given)	39261 Zerbst, Germany
DE024	(Name not given, since no consent given)	07407 Rudolstadt, Germany
DE025	(Name not given, since no consent given)	10969 Berlin, Germany
DE026	(Name not given, since no consent given)	Germany
DE028	(Name not given, since no consent given)	14089 Berlin, Germany
DE029	(Name not given, since no consent given)	04103 Leipzig, Germany

5 PUBLICATION OF TRIAL RESULTS IN MEDICAL JOURNALS

The results of the KF5503/53 clinical trial have been published in the following medical journals:

Sabatowski R, Böhme F, Steigerwald I. Evaluation of driving ability in patients with severe, chronic low back pain or osteoarthritis knee pain on stable treatment with tapentadol prolonged release. Poster presented at the International Association for the Study of Pain (IASP) 14th World Congress of Pain, August 27-31, 2012, Milan, Italy.

Sabatowski R, Scharnagel R, Gyllensvärd A, Steigerwald I. Driving ability in patients with severe chronic low back or osteoarthritis knee pain on stable treatment with tapentadol prolonged release: a multicenter, open-label, Phase 3b trial. Pain Ther 2014; 3 (1) 17-29.