TITLE OF TRIAL: A randomized, double-blind, parallel-arm, placebo- and comparator-controlled trial of the efficacy and safety of multiple doses of immediate-release (IR) CG5503 for post-operative pain following abdominal hysterectomy

SPONSOR/COMPANY: Grünenthal, Zieglerstrasse 6, 52078 Aachen, Germany

COORDINATING INVESTIGATOR: [redacted] 20-954 Lublin, Poland

TRIAL CENTRES: In total 52 centers; 4 in Hungary, 4 in Lativa, 10 in Poland, 12 in Romania, 5 in Slovakia, 1 in Slovenia, 5 in the Ukraine, 7 in Russia, 4 in Serbia.

PUBLICATION (REFERENCE): Not applicable.

TRIAL PERIOD (YEARS):

First subject enrolled:	19 May 2007
Last subject completed:	11 Mar 2008
Data base lock:	01 Apr 2008

PHASE OF DEVELOPMENT: III

INVESTIGATIONAL MEDICINAL PRODUCTS: Tapentadol (CG5503 base) IR 50 mg, 75 mg, or 100 mg, morphine IR 20 mg, or placebo

OBJECTIVES:

The main objectives were to demonstrate the efficacy and safety of multiple-dose application of 3 different oral doses of tapentadol IR compared to placebo in women undergoing abdominal hysterectomy.

Further objectives of this trial were:

- To evaluate the tolerability of 3 different oral doses of tapentadol IR compared to placebo.
- To evaluate the tolerability of 3 different oral doses of tapentadol IR compared to morphine IR.
- To explore the multiple-dose analgesic efficacy of 3 different oral doses of tapentadol IR compared to morphine IR.
- To describe the pharmacokinetics of tapentadol IR in the trial population.

METHODOLOGY: Randomized, multi-center, double-blind, placebo- and comparator-controlled, parallel-arm, dose response Phase III trial.

Following a Screening and Enrollment Period (Day –28 to Day –1), subjects entered hospital for a Pre-Operative Visit (Day -1) and subsequent abdominal hysterectomy. Subjects could qualify for further participation on the day after surgery on Day 1 (Qualification Period) between 04:00 and 10:00 (no more than 6 hours after the last possible administration of post-operative morphine s.c.). The Double-Blind Period started immediately following random assignment of subjects to a

treatment group and lasted for up to 72 hours. A Follow-up Visit was performed 4 days to 14 days following the last administration of the investigational medicinal product (IMP).

During the Double-Blind Period, subjects received identically appearing capsules of IMP containing either tapentadol IR 50 mg, 75 mg, or 100 mg, morphine IR 20 mg, or placebo. The IMP was administered as a single, oral dose once every 4 hours to 6 hours (subjects were allowed to take their next dose as early as 4 hours, but no later than 6 hours after the previous dose). Additionally, in case of insufficient pain relief, subjects were allowed to take their second dose of trial medication between 1 hour to 6 hours after the first dose on Day 1.

Pharmacokinetics, efficacy, and safety were assessed during the Double-Blind Period.

NUMBER OF SUBJECTS:

Treatment group	Planned	Randomized	Safety set	Evaluated Intention to treat set	Per protocol set
Placebo	171	169 (100%)	169 (100%)	166 (98.2%)	164 (97.0%)
Tapentadol IR 50 mg	171	168 (100%)	168 (100%)	163 (97.0%)	159 (94.6%)
Tapentadol IR 75 mg	171	171 (100%)	171 (100%)	167 (97.7%)	161 (94.2%)
Tapentadol IR 100 mg	171	176 (100%)	176 (100%)	172 (97.7%)	166 (94.3%)
Morphine IR 20 mg	171	170 (100%)	170 (100%)	164 (96.5%)	156 (91.8%)

NUMBER OF DISCONTINUATIONS:

	Reason for trial discontinuation			
Treatment group	Adverse events	Lack of efficacy	Other reasons	Total
Placebo	6 (3.6%)	41 (24.3%)	8 (4.6%)	55 (32.5%)
Tapentadol IR 50 mg	7 (4.2%)	10 (6.0%)	7 (4.1%)	24 (14.3%)
Tapentadol IR 75 mg	8 (4.7%)	4 (2.3%)	8 (4.7%)	20 (11.7%)
Tapentadol IR 100 mg	14 (8.0%)	5 (2.8%)	11 (6.2%)	30 (17.0%)
Morphine IR 20 mg	11 (6.5%) [a]	11 (6.5%)	13 (7.6%)	35 (20.6%)

a) According to the adverse event data, 12 subjects (7.1%) had adverse events that led to trial discontinuation, however, this was the primary reason for discontinuation from the trial in only 11 subjects (6.5%).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Non-pregnant, non-lactating female subjects aged between 18 years and 80 years of age with a scheduled abdominal hysterectomy with or without bilateral salpingo-oophorectomy due to uterine leiomyomas, dysfunctional uterine bleeding, or endometrial hyperplasia were eligible for this trial. Subjects qualified to enter the trial if pain reached ≥4 on the 11 point numerical rating scale (NRS) and moderate to severe pain on a verbal rating scale (VRS) within 6 hours following the last possible application of subcutaneous morphine.

INVESTIGATIONAL MEDICINAL PRODUCTS:

Test product	Tapentadol IR, over-encapsulated tablet.
Dose	Each over-encapsulated tablet contains 58 mg, 87 mg, or 116 mg of tapentadol hydrochloride corresponding to 50 mg, 75 mg, or 100 mg tapentadol.
Mode of administration	Second oral dose of trial medication within 1 hour to 6 hours after the first dose. All subsequent oral doses were to be taken every 4 hours to 6 hours after the previous dose.
Batch number	PD2225 (50 mg); PD2226 (75 mg); PD2227 (100 mg).
Duration of treatment	Day 1 to Day 3.
Placebo	Placebo to match tapentadol IR over-encapsulated tablets, and morphine IR over-encapsulated tablets.
Dose	Not applicable.
Mode of administration	Second oral dose of trial medication within 1 hour to 6 hours after the first dose. All subsequent oral doses were to be taken every 4 hours to 6 hours after the previous dose.
Batch number	PD2244.
Duration of treatment	Day 1 to Day 3.
Comparator	Morphine sulfate, immediate-release formulation (IR), over-encapsulated tablets.
Dose	Each over-encapsulated tablet contains 20 mg morphine sulfate.
Mode of administration	Oral administration of 20 mg per dose. Second oral dose of trial medication within 1 hour to 6 hours after the first dose. All subsequent oral doses were to be taken every 4 hours to 6 hours after the previous dose.
Batch number	E04584-004E
Duration of treatment	Day 1 to Day 3

CRITERIA FOR EVALUATION:

Efficacy

Efficacy assessments included sum of pain intensity difference (SPID) at 6, 12, 24, 48, and 72 hours, total pain relief (TOTPAR) at 6, 12, 24, 48, and 72 hours, responder rates at 12, 24, 48, and 72 hours, sum of total pain relief and pain intensity difference (SPRID) at 6, 12, 24, 48, and 72 hours, Patient Global Impression of Change (PGIC) at 24 and 72 hours, and the time to first use of additional analgesic medication. The primary efficacy variable for this trial was $SPID_{24}$ calculated relative to the date and time of first dose. The key secondary efficacy variable for this trial was $SPID_{48}$ calculated relative to the date and time of first dose.

Safety

Adverse events were recorded from the time that the trial informed consent form was signed, just before the first trial-related procedure, until trial termination or definite outcome. Other safety evaluations included findings from clinical and hematological laboratory testing, physical examination, vital signs, and 12-lead electrocardiograms.

Pharmacokinetics

Venous blood samples of 4 mL were collected for the determination of serum concentrations of tapentadol and optionally of morphine. In total, 5 samples were collected. Three samples were collected from all subjects on Day 1 prior to the first dose of IMP and at approximately 1 hour and 3 hours after the first IMP administration. For Day 2 and Day 3, subjects were randomly allocated to 1 of 2 analysis groups to assess pharmacokinetic parameters. Two blood samples were drawn from one-half of the subjects on Day 2, and from the other half of the subjects on Day 3. Blood samples were collected prior to and at approximately 2 hours after the third IMP administration of the respective day.

STATISTICAL METHODS:

Demographic and baseline characteristics, drug exposure, trial completion or discontinuation and reasons for discontinuation were summarized by treatment.

The primary efficacy analysis population comprised all randomized subjects who took at least 1 dose of IMP and had a baseline pain assessment (intent-to-treat [ITT]). The analyses of main interest for the efficacy parameters were based on the ITT.

The primary endpoint, $SPID_{24}$, was calculated as the weighted sum of the scheduled pain intensity difference (difference between baseline in the Qualifying Period and current pain intensity) collected up to 24 hours after the first dose of IMP. Last observation carried forward was used to impute scheduled pain assessments following early discontinuation from the trial or after first intake of additional analgesic medication. The $SPID_{24}$ was analyzed using an analysis of covariance model with treatment and analysis site as factors and baseline pain intensity score as a covariate. The Hochberg's procedure was used to adjust the p-values to control for the multiplicity due to comparison of each tapentadol IR group with placebo. The sensitivity of the primary efficacy results to the imputation strategy used was evaluated by re-analyzing the primary endpoint using different imputation rules [such as Baseline Observation Carried Forward (BOCF)]. Intermittent missing pain intensity scores were imputed using a linear interpolation approach.

The key secondary endpoint, $SPID_{48}$, was calculated and analyzed in a similar manner to the $SPID_{24}$ but using the pain intensity difference values collected up to 48 hours after the first dose of IMP. A stepwise strategy was used to control the overall level of significance for both the primary and key secondary endpoints at 0.05 by conditioning the analysis of the key secondary endpoint on the results of the primary endpoint analysis; only those comparisons of tapentadol IR versus placebo that were statistically significant on the primary endpoint were analyzed for the key secondary endpoint.

A similar weighted summation approach to that of the primary endpoint was employed to calculate SPID at 6, 12, and 72 hours as well as TOTPAR and SPRID at 6, 12, 24, 48, and 72 hours. Descriptive statistics for all PAR, PID, PRID, TOTPAR, SPID, and SPRID variables were provided for each treatment group.

The percent change from baseline in pain intensity at rest at 24 hours was calculated using an 11-point NRS. Subjects without a pain value at 24 hours, or those who used additional analgesics prior to 24 hours were assigned a score of 0%. The responder rate for a given percent change value was defined as the proportion of subjects with a value greater than the defined threshold. A comparison of the distribution of responder rates between treatments was performed using a log-rank test stratified by analysis site. Response rates for achieving 30% and 50% improvement in pain intensity relative to baseline were statistically compared using the Cochran-Mantel-Haenszel test stratified by analysis site.

The distributions of the time to first additional analgesic medication were estimated by the Kaplan-Meier approach and treatments compared using the log-rank test stratified by analysis site.

The PGIC assessment was summarized descriptively and compared with placebo using the Cochran-Mantel-Haenszel test stratified by analysis site.

Treatment-emergent adverse events were summarized for each treatment group by System Organ Class and Preferred Term according to the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory data (including changes from baseline) were descriptively summarized at each scheduled time-point by the type of laboratory test. Normal reference ranges were used for the summary of shifts relative to baseline for each laboratory parameter. The 12-lead electrocardiogram and vital sign results were summarized (including change from baseline) by parameter and scheduled time point.

Serum concentrations for tapentadol, morphine, and its metabolite morphine-6-glucuronide were descriptively summarized by time-point.

SUMMARY:

Efficacy results:

Overall, demographic and baseline characteristics were similar across all treatment groups.

The results of the trial were robust in demonstrating the efficacy of tapentadol IR 50 mg, 75 mg, and 100 mg with statistically significant improvements in pain relief demonstrated for each dose of tapentadol IR compared to placebo on the primary, key secondary, and all secondary efficacy variables, except for the time to perceptible pain relief, the time to meaningful pain relief, and the time to onset of analgesia. The efficacy of morphine IR 20 mg was similar to that of tapentadol IR 75 mg based on analysis of the primary and key secondary endpoints over a 24-hour and 48-hour period respectively.

All tapentadol treatment groups showed statistically significant improvement in pain relief compared to the placebo group for the primary endpoint, SPID24 (all Hochberg-adjusted p-values <0.0001). In addition, there was a numerical trend of increasing efficacy with increasing tapentadol IR dose (LS-mean differences to placebo of 18.1, 20.8, and 23.3 for tapentadol IR 50 mg, 75 mg and 100 mg respectively); however, the magnitude of the difference between the tapentadol groups was small.

Morphine IR 20 mg demonstrated a statistically significant improvement in pain compared with the placebo group based on the primary endpoint, SPID24 ($p < 0.0001$), thereby confirming the sensitivity of the trial (LS-mean difference to placebo of 20.6).

All tapentadol treatment groups showed statistically significant improvement in pain relief compared to the placebo group for the key secondary variable, SPID48 (all Hochberg-adjusted p-values <0.001). In addition, there was a numerical trend of increasing efficacy with increasing tapentadol IR dose (LS-mean differences to placebo of 37.1, 44.0, and 51.4 for tapentadol IR 50 mg, 75 mg, and 100 mg respectively). Morphine IR 20 mg also demonstrated a statistically significant improvement in pain compared with the placebo group (p <0.0001) (LS-mean difference to placebo of 46.9).

There was a statistically significant difference in the distributions of time to first additional analgesic medication (all Hochberg-adjusted p <0.0001), with longer times to the need for additional analgesics for each dose of tapentadol IR versus placebo. In addition, there was a numerical trend for decreasing use of additional analgesic with increasing tapentadol IR dose.

Statistically significant differences were observed between each dose of tapentadol IR and placebo in the distribution of responder rates based on pain intensity at 24 hours (all p <0.0001). The percentage of subjects who showed at least 30% improvement in pain intensity at 24 hours was 53.6% in the placebo group, compared to 71.2% to 73.3% in the tapentadol IR groups (all p-values versus placebo ≤0.0001). The percentage of subjects who showed at least 50% improvement in pain intensity at 24 to hours was 38.0% in the placebo group, compared to 58.9% to 62.9% in the tapentadol IR groups (all p-values versus placebo <0.0001). Similar results, albeit with a higher response rate for each treatment group, were observed at 48 hours.

Fewer subjects on placebo (81.3%) experienced onset of analgesia, compared to subjects in the tapentadol IR groups (89.6% to 91.6%), although no statistically significant differences relative to placebo were observed.

The rating of PGIC by the subjects at 24 hours was similar in the tapentadol IR groups, and was indicative of a greater benefit than in the placebo group. The distribution of responses was statistically significantly different from placebo (all p <0.0001). At 72 hours, the findings were similar to those observed at 24 hours.

For all other secondary efficacy results (SPID at 6, 12 and 72 hours; TOTPAR at 6, 12, 24, 48, and 72 hours; SPRID at 6, 12, 24, 48, and 72 hours), each dose of tapentadol IR demonstrated a statistically significant improvement in pain relief at all time points compared with the placebo group.

As well as demonstrating a statistically significant improvement relative to placebo on the primary and key secondary endpoints, morphine IR 20 mg also demonstrated statistically significant improvements relative to placebo for all secondary endpoints, except for time to perceptible pain relief.

Safety results:

The overall incidence of treatment-emergent adverse events for the Double-Blind Period was similar for the tapentadol IR 75 mg (56.1%), 100 mg (60.2%), and the morphine IR 20 mg (58.2%) groups, but lower for both the placebo (52.1%) and the tapentadol IR 50 mg (50.0%) groups.

The most common adverse events in the active treatment groups were nausea, vomiting, constipation, and dizziness. There were no major differences in the incidence of constipation between any of the tapentadol IR treatment groups. For nausea, incidences were highest for the tapentadol IR 75 mg and 100 mg groups, whereas for vomiting and dizziness, incidences were

generally highest for the tapentadol IR 100 mg group with similar, lower incidences observed for the tapentadol IR 50 mg and 75 mg groups.

There was no difference in the incidence of gastrointestinal and central nervous system adverse events between the tapentadol IR 75 mg group and the morphine IR 20 mg group.

A higher frequency of psychiatric adverse events, e.g., anxiety, confusional state, and illusion was reported in the tapentadol IR 100 mg group, compared to patients treated with lower tapentadol doses or morphine IR 20 mg.

One death occurred during this trial in the morphine IR 20 mg group. The subject had a "disseminated lung microembolism", which was considered to be "not related" to IMP.

A total of 5 serious adverse events occurred during this trial in 4 subjects. One subject on tapentadol IR 100 mg experienced "sinus tachycardia" and "mental confusion" - these events resulted in the discontinuation of the subject from the trial. Three subjects on morphine IR 20 mg each experienced 1 serious adverse event; 1 subject each experienced "disseminated lung microembolism", "post-operative abdominal bleeding", and "bronchopneumonia". Each event led to the discontinuation of the subject from the trial and 1 event ("disseminated lung microembolism") led to the subject's death.

Six subjects on placebo, 7 subjects on tapentadol IR 50 mg, 8 subjects on tapentadol IR 75 mg, 14 subjects on tapentadol IR 100 mg, and 12 subjects on morphine IR 20 mg reported treatment-emergent adverse events that lead to trial discontinuation.

There were few potentially clinically important findings in laboratory values, vital signs or ECGs based on the pre-defined criteria.

CONCLUSION:

All doses of tapentadol IR were statistically superior to placebo in relieving moderate to severe pain after hysterectomy. The outcome of the primary, key secondary, and most other secondary endpoints supported the conclusion of robustness of efficacy of tapentadol IR 50 mg to 100 mg through 72 hours after the initiation of treatment.

Assay sensitivity was demonstrated by the statistically significant improvement in pain for the morphine IR 20 mg group compared with placebo.

The observed safety profile and types of individual adverse events for tapentadol IR 50 mg to 100 mg was in line with previous findings in clinical trials, although there were more events reported in the SOC psychiatric disorders in subjects allocated to tapentadol IR 100 mg. The reporting of these events was however similar to the reporting rate in another pain model involving major surgery.

Date of report: 15 October 2008.

ICTR SYNOPSIS SUPPLEMENT

KF5503/35

Original ICTR issue date:	15 Oct 2008	**DMS version:**	5.0
ICTR synopsis supplement date:	10 Feb 2015	**DMS version:**	1.0

1 SUPPLEMENT CONTENT

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

2 INFORMATION ABOUT PROTOCOL AMENDMENTS

There was no amendment 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
37117	(Name not given, since no consent given)	LV 1006 Riga, Latvia
37116	(Name not given, since no consent given)	LV 1001 Riga, Latvia
37118	(Name not given, since no consent given)	LV 1005 Riga, Latvia
37119	(Name not given, since no consent given)	LV 1002 Riga, Latvia
04825	(Name not given, since no consent given)	20954 Lublin, Poland
04824	(Name not given, since no consent given)	93-338 Łódź, Poland
04820	(Name not given, since no consent given)	01-809 Warszawa, Poland
04821	(Name not given, since no consent given)	02-507 Warszawa, Poland
04822	(Name not given, since no consent given)	20-081 Lublin, Poland
04826	(Name not given, since no consent given)	41-703 Ruda Śląska, Poland
04827	(Name not given, since no consent given)	40-752 Katowice, Poland
04823	(Name not given, since no consent given)	31-826 Kraków, Poland
04828	(Name not given, since no consent given)	50-528 Wrocław, Poland
04866	(Name not given, since no consent given)	91-480 Łódź, Poland
04036	(Name not given, since no consent given)	011461 Bucharest, Romania
04031	(Name not given, since no consent given)	011062 Bucharest, Romania
04029	(Name not given, since no consent given)	021659 Bucharest, Romania
04034	(Name not given, since no consent given)	010825 Bucharest, Romania
04033	(Name not given, since no consent given)	500025 Brasov, Romania
04035	(Name not given, since no consent given)	060251 Bucharest, Romania
04076	(Name not given, since no consent given)	030572 Bucharest, Romania

Site number	Investigator	Site address
04032	(Name not given, since no consent given)	050098 Bucharest, Romania
04061	(Name not given, since no consent given)	100409 Ploiesti, jud.Prahova, Romania
04075	(Name not given, since no consent given)	200642 Craiova , county Dolj, Romania
04030	(Name not given, since no consent given)	050098 Bucharest, Romania
04078	(Name not given, since no consent given)	500025 Brasov, county Brasov, Romania
42152	(Name not given, since no consent given)	83305 Bratislava, Slovak. Republic
42151	(Name not given, since no consent given)	82606 Bratislava, Slovak. Republic
42148	(Name not given, since no consent given)	97517 Banská Bystrica, Slovak. Republic
42150	(Name not given, since no consent given)	03659 Martin, Slovak. Republic
42162	(Name not given, since no consent given)	04015 Košice, Slovak. Republic
38653	(Name not given, since no consent given)	2000 Maribor, Slovenia
38056	(Name not given, since no consent given)	01034 Kiev, Ukraine
38058	(Name not given, since no consent given)	04112 Kiev, Ukraine
38055	(Name not given, since no consent given)	04210 Kiev, Ukraine
38064	(Name not given, since no consent given)	83114 Donetsk, Ukraine
38067	(Name not given, since no consent given)	69015 Zaporizhzhya, Ukraine
036-15	(Name not given, since no consent given)	Komárom 2921, Hungary
036-12	(Name not given, since no consent given)	Nyíregyháza 4400, Hungary
036-14	(Name not given, since no consent given)	4043 Debrecen, Hungary
036-13	(Name not given, since no consent given)	Békéscsaba 5600, Hungary
007-42	(Name not given, since no consent given)	St-Petersburg 194291, Russia
007-43	(Name not given, since no consent given)	St.Petersburg 194291, Russia
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007-38	(Name not given, since no consent given)	Moscow 117415, Russia
007-73	(Name not given, since no consent given)	Moscow 115093, Russia
007-71	(Name not given, since no consent given)	Belgorod 308007, Russia
381-46	(Name not given, since no consent given)	34 000 Kragujevac, Serbia
381-45	(Name not given, since no consent given)	11000 Belgrade, Serbia
381-47	(Name not given, since no consent given)	11 000 Belgrade, Serbia
381-77	(Name not given, since no consent given)	21000 Novi Sad, Serbia