TITLE OF TRIAL: A randomized, 2-arm, parallel group study assessing safety and efficacy of titrated transdermal buprenorphine in patients with moderate to severe chronic non-malignant pain

SPONSOR/COMPANY: Grünenthal GmbH, 52099 Aachen, Germany

COORDINATING INVESTIGATOR: [redacted] London EC1A 7B, United Kingdom

TRIAL CENTER(S): 23 centers in total (2 in Austria, 9 in France, 4 in Hungary, 7 in Russia and 1 in the UK)

PUBLICATION (REFERENCE): Not applicable

TRIAL PERIOD (YEARS):

First subject enrolled:	05 May 2006
Last subject completed:	03 Aug 2006
Data base lock	29 Sep 2006

PHASE OF DEVELOPMENT: III

OBJECTIVES: To assess the efficacy and tolerability of a titrated divisible buprenorphine transdermal patch in comparison to a non-titrated buprenorphine transdermal patch over 4 weeks in opioid-naïve subjects with moderate to severe chronic non-malignant pain.

METHODOLOGY: Randomized, multi-center, open-label, Transtec® [1]-controlled, parallel group, forced titration. Subjects were randomized to receive either the divisible buprenorphine transdermal patch, 10 mg for 2 weeks followed by 20 mg for 2 weeks, or Transtec® 20 mg for 4 weeks.

NUMBER OF SUBJECTS:

Treatment group	Planned	Randomized	Treated	Evaluated	
				Full analysis set (FAS)	Per protocol set (PP Set)
Buprenorphine divisible patch	123	143	143	139	98
Transtec®	123	143	143	138	92

NUMBER OF DROP-OUTS:

Treatment group	Reason for withdrawal[a]			
	AEs	Lack of efficacy	Other reasons	Total
Buprenorphine divisible patch	42	3	3	43
Transtec®	47	0	1	48

[a] Subjects may have discontinued for more than 1 reason.

[1] Transtec® is the trade name in all involved countries, except Germany, where the trade name is Transtec® PRO

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Male and non-pregnant female subjects were included, at least 18 years of age at enrollment, suffering from chronic non-malignant pain of at least 3 months duration with pain intensity >4 on an 11-point numerical rating scale (NRS) and requiring an equianalgesic dose range equivalent to 30 mg to 60 mg oral morphine per day.

INVESTIGATIONAL MEDICINAL PRODUCT(S):

Test product	Buprenorphine divisible patch
Dose	10 mg (half patch) for 2 weeks then 20 mg (full patch) for 2 weeks
Mode of administration	Transdermal
Wearing time	3.5 days/half patch or 3.5 days/full patch
Batch number	7/05770/4
Duration of treatment	4 weeks
Comparator product	Transtec®
Dose	20 mg for 4 weeks
Mode of administration	Transdermal
Wearing time	3.5 days/patch
Batch number	7/05100/5
Duration of treatment	4 weeks

CRITERIA FOR EVALUATION:

Efficacy: Pain intensity (ie, current pain) was assessed twice a day using an 11-point NRS (0 = no pain, 10 = pain as bad as can be imagined) and recorded by the subject in the diary at 8 a.m. and 8 p.m. (±1h). Subjects then rated their pain during the last 24 hours using the 11-point NRS. Subjects made a global evaluation at each visit; subjects rated their overall impression of their current pain medication as: *excellent, very good, good, fair,* or *poor*. Subjects also completed the chronic pain sleep inventory (CPSI) at each visit. Subjects recorded how often they had needed sleeping medication to help them fall asleep in the past week (*never, rarely, sometimes, usually,* or *always*) and rated their quality of sleep in the past week (*excellent, very good, good, fair,* or *poor*).

The primary efficacy endpoint was a comparison for non-inferiority of the titrated divisible buprenorphine transdermal patch versus the buprenorphine transdermal patch Transtec® based on baseline-adjusted mean pain intensity at Visit 5 (Day 27-29). The pain during the last 24 hours was used for the primary endpoint.

Safety: Criteria to assess safety were: the incidence, frequency and intensity of adverse events (AEs), and withdrawals for AEs. Vital signs and physical examination.

STATISTICAL METHODS:

Evaluation of the primary endpoint was performed by means of analysis of covariance (ANCOVA) accounting for the effects of treatment, center and baseline pain intensity. A 95% confidence interval (CI) for the difference in treatment effects (buprenorphine divisible patch minus Transtec®) was calculated. Non-inferiority of the buprenorphine divisible patch compared with Transtec® was established if the lower 95% confidence limit was greater than -1.0 units. The analyses of secondary endpoints of pain intensity used ANCOVA as described for the primary efficacy endpoint.

An analysis of variance (ANOVA) with the factors center, treatment and interaction was used to compare the average amount of rescue medication used. Additionally, the treatment-difference in average rescue medication with the respective two-sided 95% CI was calculated.

The global evaluation of the current pain medication by the subject, and the CPSI data were compared for differences between the treatments at Visits 1, 2, 3, 4 and 5 using a CMH-test adjusting for center.

The frequency of subjects with any AE (serious AE) during the trial with the respective two-sided 95% confidence limits were calculated for buprenorphine divisible patch and Transtec®. The frequency of subjects with an event was compared between buprenorphine divisible patch and Transtec® using a CMH test. The difference between buprenorphine divisible patch and Transtec® in the frequency of subjects with AEs with the respective two-sided 95% CI was calculated using an exact method based on the Binomial Z statistic. This approach was also used to examine the incidence of AEs occurring in at least 3 subjects in at least 1 treatment group.

The two-sided 95% CI for the median time to onset of AEs was calculated. Additionally the Kaplan-Meier estimator was calculated and the respective survival curves plotted. The time to onset of AEs for buprenorphine divisible patch and Transtec® were compared by a logrank test.

The incidence of withdrawal due to AEs was presented with the respective two-sided 95% confidence limits for each treatment group. The treatment groups were compared using a CMH test. The two-sided 95% CI for the median time to withdrawal due to AEs was calculated. This was based on data from only those subjects who withdrew due to AEs. Additionally the Kaplan-Meier estimator was calculated and the respective survival curves plotted. The time to withdrawal due to AEs for buprenorphine divisible patch and Transtec® were compared by a logrank test. The Kaplan-Meier analysis was based on all subjects in the Safety Set. Subjects who withdrew from the trial for a reason other than AEs were censored in this analysis at the time of withdrawal. Subjects who completed the trial were censored at the date of their last patch application.

For each of the vital signs descriptive statistics for the absolute values and the differences to baseline values were calculated at each assessment including the 95% CIs for the mean. An ANOVA was performed including the factors center, treatment, time and the interaction terms center-by-treatment and time-by-treatment. If interaction terms were not significant at the 5% level then they were removed from the model and results were based on the reduced model including factors center, treatment and visit. The time course of the mean (±SD) of respiratory rate, pulse rate and blood pressure were displayed graphically for the buprenorphine divisible patch and Transtec®.

SUMMARY:

Efficacy results:

The primary endpoint was baseline-adjusted mean pain intensity (pain in the last 24 hours) at Visit 5. Both groups showed a clinically relevant reduction in pain on the 11-point NRS, the adjusted means (accounting for baseline pain, treatment and center) were 3.97 for buprenorphine divisible patch (B-DIV) and 3.89 for Transtec® (T-PRO) for the PP Set. The difference between the treatments (B-DIV minus T-PRO) was 0.09 (95% CI: -0.55, 0.73). Hence, buprenorphine divisible patch was shown to be non-inferior to the Transtec® as the lower bound of the 95% CI was greater than the predefined non-inferiority margin of -1.0 for the PP Set and was therefore within the non-inferiority region (-1.0, ∞). This was confirmed in the FAS analysis where the treatment difference (B-DIV minus T-PRO) was -0.33 (95% CI: -0.89, 0.23).

The non-inferiority of the treatment regimen with buprenorphine divisible patch in comparison with the treatment regimen with Transtec® at Visit 5 is supported by the results given for Visit 4 (PP Set and FAS). At Visit 2 (within the titration period for buprenorphine divisible patch) the respective 95% CI for the difference between the 2 treatment regimens was not completely within the predefined non-inferiority region of (-1, ∞) for the PP Set and the FAS. At Visit 3 non-inferiority of the treatment regimen with buprenorphine divisible patch in comparison with the treatment regimen with Transtec® was confirmed for the PP Set but not the

FAS. Both treatment groups experienced clinically relevant pain relief at Visit 2: adjusted mean for the PP Set was 2.14 for the buprenorphine divisible patch group (receiving 10 mg buprenorphine patch) and 2.62 for the Transtec® group (receiving 20 mg buprenorphine patch).

Similarly, non-inferiority of the treatment regimen with buprenorphine divisible patch in comparison to the treatment regimen with Transtec® at Visit 5 was also supported by the results given for current pain in the morning and evening at Visits 3 and 4 (PP Set and FAS). The respective 95% CIs were not completely within the predefined non-inferiority region of (-1, ∞) for pain in the morning (FAS) and evening (PP Set and FAS) only at Visit 2, when the buprenorphine divisible patch group had slightly lower pain relief scores than the Transtec® group.

There were 3 (2.2%) subjects who withdrew due to lack of efficacy in the buprenorphine divisible patch group and 0 in the Transtec® group.

As could be anticipated, the buprenorphine divisible patch group was taking more rescue medication during the buprenorphine divisible patch titration phase, Days 1 to 14, than the Transtec® group (the mean difference for B-DIV minus T-PRO was 0.295 tablets per day for the PP Set) but during Days 15 to 29, after titration was completed, the use of rescue medication was very similar for the 2 groups.

The patients' global evaluation of treatment indicated no relevant difference between the treatments, except at Visit 5 for the PP Set, with more subjects recording their treatment as *excellent/very good/good* in the Transtec® group than in the buprenorphine divisible patch group (85.9% versus 73.5%, respectively). This difference was not confirmed by the analysis of the FAS.

There were no relevant differences between the treatments for the PP Set or the FAS at any visit for the CPSI questionnaire assessing the use of sleeping medication. In both groups, the majority of subjects *never* or *rarely* took sleeping medication. Likewise, there were no relevant differences between the treatments for the PP Set or the FAS at any visit for quality of sleep, which improved in both groups during the trial.

Safety results:

A total of 245 subjects reported at least 1 treatment-emergent AE during the whole trial period: 122 subjects (85.3%) in the buprenorphine divisible patch group and 123 subjects (86.0%) in the Transtec® group. During Days 1 to 14, 105 subjects (73.4%) in the buprenorphine divisible patch group and 113 subjects (79.0%) in the Transtec® group had at least 1 AE. The mean time to first AE was 4.9 days (SD 6.97) in the buprenorphine divisible patch group and 3.5 days (SD 5.88) in the Transtec® group; the median value was 1.0 days in both groups.

The most common AEs during Days 1 to 14 were nausea, vomiting, somnolence and dizziness. In general, the incidence of AEs reported by ≥ 2.0% of subjects was similar for the 2 groups during Days 1 to 14, except for nausea, somnolence and constipation, which were each reported at a lower incidence in the buprenorphine divisible patch group than in the Transtec® group (nausea was reported for 35.0% of subjects in the buprenorphine divisible patch group versus 46.2% in the Transtec® group, somnolence was reported for 18.2% of subjects in the buprenorphine divisible patch group versus 26.6% in the Transtec® group and constipation was reported for 10.5% of subjects in the buprenorphine divisible patch group versus 19.6% in the Transtec® group).

Considering the whole trial period (ie, Days 1 to 29), the most common AEs were nausea, vomiting, somnolence, dizziness and constipation. In general the incidence of AEs reported by ≥ 2.0% of subjects was similar for the 2 groups, with the following exceptions: nausea, somnolence and constipation were reported less frequently in the buprenorphine divisible patch group than in the Transtec® group (nausea was reported for 40.6% of subjects in the buprenorphine divisible patch group versus 47.6% in the Transtec group; somnolence was reported for 23.1% of subjects in the buprenorphine divisible patch group versus 30.8% of the subjects in the Transtec® group; constipation was reported for 15.4% of subjects in the buprenorphine divisible patch group versus 23.8% in the Transtec® group). Headache and diarrhea were reported more

frequently in the buprenorphine divisible patch group than in the Transtec® group (headache was reported for 15.4% of subjects in the buprenorphine divisible patch group versus 9.1% in the Transtec® group; diarrhea was reported for 6.3% of subjects in the buprenorphine divisible patch group versus 0.7% in the Transtec® group). Further AEs typical for opioids were reported at the following similar incidences in each group: dizziness 21.7% of subjects in the buprenorphine divisible patch group versus 24.5% in the Transtec® group, respectively, and vomiting 30.1% of subjects versus 25.9%, respectively.

Most AEs were considered at least possibly related to IMP. Concerning intensity, most AEs were mild or moderate. For vital signs and physical examination no relevant differences were detected between the treatment groups.

One subject in the Transtec® group had 8 SAEs reported (vertigo, nausea (2x), vomiting (2x), circulatory collapse, trigeminal neuralgia (2x), which were expected and typical for the buprenorphine patch, except trigeminal neuralgia where the relationship to Transtec® was assessed as unlikely.

Fewer subjects withdrew due to somnolence in the buprenorphine divisible patch group than the Transtec® group (5.6% versus 11.9%, respectively) and nausea (14.0% versus 23.1%, respectively). Overall, 42 subjects (29.4%) in the buprenorphine divisible patch group and 47 (32.9%) in the Transtec® group withdrew due to AEs. The mean time to withdrawal due to AE was 10.8 days (SD 7.81) in buprenorphine divisible patch group and 8.0 days (SD 4.77) in the Transtec® group; the median value was 7.0 days (95% CI: 7.0, 9.0 days) in the buprenorphine divisible patch group and 7.0 days (95% CI: 6.0, 8.0 days) in the Transtec® group.

CONCLUSION: The buprenorphine divisible patch was non-inferior to Transtec® with regard to efficacy in opioid naïve subjects with moderate to severe chronic non-malignant pain (mostly back pain or osteoarthritis). The analysis of the secondary endpoints supported the results of the primary endpoint. The buprenorphine divisible patch was well tolerated with a safety profile in line with that of Transtec®. During the titration phase for buprenorphine divisible patch group, the incidences of nausea, somnolence and constipation were lower than for the Transtec® group. The difference in incidence for nausea, somnolence and constipation was still evident between the treatment groups when the whole trial period was considered. The incidences of severe somnolence and somnolence leading to withdrawal were decreased with the buprenorphine divisible patch in comparison with Transtec®. The rate of withdrawal due to AE was slightly lower in the buprenorphine divisible patch group than in the Transtec® group. Together with the lower incidences of certain opioid-typical AEs seen in the titrated population, this indicates an improvement of tolerability with the buprenorphine divisible patch.

Date of report: 09 Jul 2007

ICTR SYNOPSIS SUPPLEMENT

KF5303/01

Original ICTR issue date:	09 Jul 2007	**DMS version:**	3.0
ICTR synopsis supplement date:	24 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

The protocol was amended on 09 Jan 2006 to remove inconsistencies; this amendment did not alter the trial design or conduct, so that a new ethics committee appraisal was not necessary before the amendments could be implemented. The ethics committees were informed about the amendment.

Amendment 1 of 09 Jan 2006

The following changes were made to clarify and correct inconsistent information in the protocol:

- Study title on the Patient Card was changed to match the protocol title
- Text was amended to reflect that rescue medication would be dispensed for 2 weeks as well and for the sake of clarity (protocol Sections 6.4.2 to 6.4.5)
- Protocol Section 6.9: Acceptable methods of contraception were adapted to match inclusion criterion
- Table was amended to clarify the packaging of IMP (protocol Section 7.1.2)
- Information on time needed to elapse before patch was applied to same skin site was amended (protocol Section 7.1.3)
- Information on prohibited medication was changed to match exclusion criterion (protocol Section 7.2.1)
- Information on initials was deleted as initials were not collected (protocol Sections 8.3 and 10.9)
- The table in Section 9.2 of the protocol was updated to provide clarification
- Flow chart was adapted to match the visit schedule (protocol Appendix I)

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
AT-001	(Name not given, since no consent given)	1090 Vienna, Austria
AT-002	(Name not given, since no consent given)	1020 Vienna, Austria
FR-001	(Name not given, since no consent given)	F-69003 Lyon, France

Site number	Investigator	Site address
FR-002	(Name not given, since no consent given)	F-33530 Bassens, France
FR-003	(Name not given, since no consent given)	F-49125 Briollay, France
FR-004	(Name not given, since no consent given)	F-79100 Thouars, France
FR-005	(Name not given, since no consent given)	F-49610 Murs Erigne, France
FR-006	(Name not given, since no consent given)	F-5300 Laragne, France
FR-007	(Name not given, since no consent given)	F-49500 Segré, France
FR-010	(Name not given, since no consent given)	Moutiers, 54660, France
FR-011	(Name not given, since no consent given)	Jarny, 54800, France
HU-001	(Name not given, since no consent given)	4043 Debrecen, Hungary
HU-002	(Name not given, since no consent given)	2500 Esztergom, Hungary
HU-003	(Name not given, since no consent given)	5200 Gyula, Hungary
HU-004	(Name not given, since no consent given)	5000 Szolnok, Hungary
RU-001	(Name not given, since no consent given)	115522 Moscow, Russia
RU-004	(Name not given, since no consent given)	603033 Nizhniy Novgorod, Russia
RU-005	(Name not given, since no consent given)	194291 St Petersburg, Russia
RU-006	(Name not given, since no consent given)	105229 Moscow, Russia
RU-007	(Name not given, since no consent given)	214018 Smolensk, Russia
RU-010	(Name not given, since no consent given)	196247 St Petersburg, Russia
RU-013	(Name not given, since no consent given)	194195 St Petersburg, Russia
UK-001	(Name not given, since no consent given)	EC 1A 7BE London, United Kingdom