Clinical trial results:
Open-label, single-arm, flexible dosing, Phase III trial, with oral tapentadol prolonged release (PR) in subjects with chronic malignant tumor-related pain who have completed the Maintenance Period of the KF 5503/15 trial.

Summary

EudraCT number	2009-013291-46
Trial protocol	CZ AT ES HU FR BG RO
Global end of trial date	08 May 2014

Results information

Result version number	v1 (current)
This version publication date	25 February 2016
First version publication date	19 June 2015

Trial information

Trial identification

Sponsor protocol code	KF5503/52

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01264887
WHO universal trial number (UTN)	-
Other trial identifiers	Grünenthal GmbH: 168935

Notes:

Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr. 6, Aachen, Germany, 52099
Public contact	Grünenthal Clinical Trial Helpdesk, Grünenthal Clinical Trial Helpdesk, 49 241 569 3223 , Clinical-Trials@grunenthal.com
Scientific contact	Grünenthal Clinical Trial Helpdesk, Grünenthal GmbH, 49 241 569 3223 , Clinical-Trials@grunenthal.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 May 2014
Global end of trial reached?	Yes
Global end of trial date	08 May 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The characterization of the long term safety profile of tapentadol PR at doses ranging from 100 mg to 250 mg taken twice daily, in patients with malignant tumor-related pain

Protection of trial subjects:

The trial was conducted according to ICH-GCP guidelines, the applicable local laws, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki.
Regulatory authorities were notified of the trial and amendments as required by national regulations, and where necessary relevant authorization was obtained.
Furthermore, the competent authorities were notified of this trial in accordance with national requirements.

Background therapy:

The use of concomitant medication was reported by all subjects.

The participating sites could prescribe standard medications, for example, for breakthrough pain, nausea, vomiting, and constipation. These medications were recorded in the case report form.
For subjects on tapentadol treatment, caution was to be exercised if concomitant drug administration of strong enzyme inducing drugs (e.g., rifampicin, phenobarbital, St John's Wort [hypericum perforatum]) started or stopped, since this may have led to decreased efficacy or risk for adverse effects, respectively.

Subjects had to adhere to the following precautions:
• As with other centrally acting analgesics, subjects were to be advised not to drink alcohol or take other central nervous system suppressants concomitantly with tapentadol PR.
• Because tapentadol may cause symptoms typical of a centrally acting analgesic, such as fatigue, dizziness, nausea, or vertigo, subjects were to be advised that operating machinery or driving a vehicle may be dangerous.

Monoamine oxidase inhibitors were prohibited during the trial.
Radiotherapy and treatment by a pain-inducing chemotherapy protocol (as judged by the investigator) were forbidden for all patients for 30 days prior to enrollment and during the trial. However, it was up to the evaluation of the investigator if the chemotherapy was pain-inducing and so, if a potentially pain-inducing substance was well tolerated in previous chemotherapy cycles, the patient could be included even if a new cycle with this substance was planned during the trial.

Evidence for comparator: -

Actual start date of recruitment	03 March 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Romania: 5

Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Serbia: 6
Country: Number of subjects enrolled	Moldova, Republic of: 6
Country: Number of subjects enrolled	Russian Federation: 3
Worldwide total number of subjects	31
EEA total number of subjects	16

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	25
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First subject was enrolled on the 03 March 2011 and the last subject completed the trial on the 08 May 2014. Subjects had to have completed the Maintenance period in the KF5503/15 trial to enter the KF5503/52 trial.

Pre-assignment

Screening details:

Subjects directly entered the KF5503/52 trial from the KF5503/15 trial, i.e., within 7 days of the final visit in the KF5503/15 trial. Alternatively subjects with a gap of more than 7 days and less than 24 weeks had additional visit to assess eligibility into the KF5503/52 trial.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Tapentadol prolonged release

Arm description:

Subjects received doses between 100 to 250 mg tapentadol twice daily (50 and 100 mg tablets to be dispensed). A flexible titration to achieve sufficient pain relief to continue with effective analgesia for as long as the subject tolerates and wished to continue treatment was permited.

Arm type	Experimental
Investigational medicinal product name	Tapentadol prolonged release
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The medication was supplied in blister cards suitable for 10 days intake allowing dose adjustment from 100 mg taken twice daily to 250 mg taken twice daily.

Number of subjects in period 1	Tapentadol prolonged release
Started	31
Completed	2
Not completed	29
Adverse event, serious fatal	7
Consent withdrawn by subject	6
Physician decision	4
Adverse event, non-fatal	5
Not specified	2
Lack of efficacy	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	31	31	
Age categorical Units: Subjects			
Adults (18-64 years)	25	25	
From 65-84 years	6	6	
Age continuous Units: years			
arithmetic mean	55.8		
standard deviation	± 11.91	-	
Gender categorical Units: Subjects			
Female	16	16	
Male	15	15	
Weight Units: kilogram(s)			
arithmetic mean	64.6		
standard deviation	± 16.45	-	
Height Units: meter			
arithmetic mean	165		
standard deviation	± 10.24	-	
Body Mass Index Units: kilogram(s)/square meter			
arithmetic mean	23.6		
standard deviation	± 4.79	-	

End points

End points reporting groups

Reporting group title	Tapentadol prolonged release

Reporting group description:

Subjects received doses between 100 to 250 mg tapentadol twice daily (50 and 100 mg tablets to be dispensed). A flexible titration to achieve sufficient pain relief to continue with effective analgesia for as long as the subject tolerates and wished to continue treatment was permited.

Primary: Severity of Adverse Events

End point title	Severity of Adverse Events[1]

End point description:

A treatment emergent adverse event (TEAE) was any adverse event that occurred after the first administration of IMP, or any pre-existing adverse event that worsened (e.g., in intensity, frequency, or quality) after the first administration of IMP, up to 3 days for serious adverse events and up to 30 days for deaths after last intake of tapentadol prolonged release.

The clinical "intensity" of adverse event were classified as:
Mild: signs and symptoms which can be easily tolerated. Symptoms could be ignored and disappeared when the participant is distracted.
Moderate: symptoms caused discomfort but were tolerable, they could not be ignored and affect concentration.
Severe: symptoms affected the usual daily activity.

End point type	Primary

End point timeframe:

Day 1; up to 144 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoints for this trial are the frequency and severity of AEs at recorded the visits during the Open-label Treatment Period and the Follow-Up Visit. These will be described to assess long term safety and no statistical testing or inference is planned on this primary objective.

End point values	Tapentadol prolonged release			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Subjects				
mild intensity	3			
moderate intensity	15			
severe intensity	12			

Statistical analyses

No statistical analyses for this end point

Primary: Relatedness Assessment of Treatment Emergent Adverse Events

End point title	Relatedness Assessment of Treatment Emergent Adverse Events[2]

End point description:

Participant-based analysis of treatment emergent adverse events (TEAEs) regarding the relationship to the study drug (tapentadol). The TEAEs were reported by the participants or were captured by the investigator. The relationship was rated by the investigator. The categorization of relatedness into one of the two categories was based on the following: Related included "possible", "probable/likely", and "certain"; whilst unrelated treatment emergent adverse events include those rated by the investigator as "unlikely", "conditional/unclassified", "un-assessable/unclassifiable", and "not related".

End point type	Primary

End point timeframe:

Day 1; up to 144 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoints for this trial are the frequency and severity of AEs at recorded the visits during the Open-label Treatment Period and the Follow-Up Visit. These will be described to assess long term safety and no statistical testing or inference is planned on this primary objective.

End point values	Tapentadol prolonged release			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Subjects				
No Treatment Emergent Adverse Events	1			
All Treatment Emergent Adverse Events	30			
Investigator-rated Related	6			
Investigator-rated Not Related	24			

Statistical analyses

No statistical analyses for this end point

Primary: Countermeasures Taken Due to Treatment Emergent Adverse Events

End point title	Countermeasures Taken Due to Treatment Emergent Adverse Events[3]

End point description:

Participant-based analysis of treatment emergent adverse events (TEAEs) regarding countermeasure to the study drug (tapentadol). The TEAEs were reported by the participants or were captured by the investigator. The countermeasure taken by the investigator were reported.

End point type	Primary

End point timeframe:

Day 1; up to 144 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoints for this trial are the frequency and severity of AEs at recorded the visits during the Open-label Treatment Period and the Follow-Up Visit. These will be described to assess long term safety and no statistical testing or inference is planned on this primary objective.

End point values	Tapentadol prolonged release			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Subjects				
All Treatment Emergent Events	30			
No Treatment Emergent Adverse Events	1			
No countermeasures taken	5			
Countermeasures with Medication	17			
Trial Discontinued Countermeasure	6			
Other Countermeasure due to Somnolence	1			
Other Countermeasure due to Migraine	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Assess Consumption of Tapentadol During Long Term Use

End point title	Assess Consumption of Tapentadol During Long Term Use

End point description:

All participants from the KF5503/15 that enrolled into this trial were on tapentadol prolonged release.

Participants were dosed in the range of 100 to 250 mg tapentadol twice daily. The dose was titrated to achieve sufficient pain relief to continue with effective analgesia for as long as the participant tolerated and wishes to continue treatment.

Summary of the modal total daily dose during the treatment period. The modal dose was based on assessment of the consecutive morning and evening intake amounts on each day and evaluation of the total daily dose.

No participant received more than 500 mg per day.

End point type	Secondary

End point timeframe:

Day 1; up to 144 weeks

End point values	Tapentadol prolonged release			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Subjects				
less than 200 mg/day	0			
200 to less than 250 mg/day	3			
250 to less than 300 mg/day	1			
300 to less than 350 mg/day	8			
350 to less than 400 mg/day	0			
400 to less than 450 mg/day	11			
450 to less than 500 mg/day	0			
500 mg/day	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Tapentadol Prolonged Release Exposure

End point title	Tapentadol Prolonged Release Exposure

End point description:

The number of days that participants took tapentadol prolonged release. The extent of exposure was categorized into 2 periods, less than 90 days and more than 90 days (up to 144 weeks).

End point type	Secondary

End point timeframe:

Day 1; up to 144 weeks

End point values	Tapentadol prolonged release			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Subjects				
Tapentadol exposure from 1 to 90 days	11			
Tapentadol exposure for more than 90 days	20			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Average Pain Intensity (Over a Twelve-week Period)

End point title	Average Pain Intensity (Over a Twelve-week Period)

End point description:

The participant scored their pain intensity on an 11-point Numerical Rating Scale (NRS) where a score of 0 indicated "no pain" and a score of 10 indicated "pain as bad as you can imagine".
Average pain intensity score is the average of pain experienced for previous 24 hours as rated on an 11-point NRS at each visit. Calculations are based on 3 consecutive planned (at 4-weekly intervals) visits.

End point type	Other pre-specified

End point timeframe:

Day 1; up to Week 144

End point values	Tapentadol prolonged release			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: 11-point Numerical Rating Scale (NRS)				
arithmetic mean (standard deviation)				
Baseline (N=31)	3.3 (± 1.79)			
Week 1 to 12 (N =30)	3.1 (± 1.95)			
Week 13 to 24 (N=20)	3.1 (± 2.51)			
Week 25 to 36 (N=14)	2.1 (± 1.57)			
Week 37 to 48 (N=13)	2 (± 1.71)			
Week 49 to 60 (N=11)	2 (± 1.78)			
Week 61 to 72 (N=9)	2 (± 1.61)			
Week 73 to 84 (N=8)	2.4 (± 1.97)			
Week 85 to 96 (N=7)	3.1 (± 3.16)			
Week 97 to 108 (N=6)	3.1 (± 3.76)			
Week 109 to 120 (N=3)	3.3 (± 2.52)			
Week 121 to 132 (N=1)	1 (± 0)			
Week 133 to 144 (N=1)	1 (± 0)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Average Daily Total Tapentadol Prolonged Release Dose

End point title	Average Daily Total Tapentadol Prolonged Release Dose

End point description:

The Total Daily Dose (TDD) on any given day is the sum of the morning and evening intake amounts. The average TDD is an individuals average over the trial period.

End point type	Other pre-specified

End point timeframe:

Day 1; up to 144 weeks

End point values	Tapentadol prolonged release			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: milligram(s)/24 hours				
arithmetic mean (standard deviation)				
Average Daily Total Tapentadol PR dose	360 (± 91.21)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 (Day of first open-label dose, i.e. first tapentadol PR intake during the treatment phase, up to 30 days after last intake of open-label tapentadol prolonged release) to 144 weeks.

Adverse event reporting additional description:

A treatment emergent adverse event is defined as any adverse event that occurred for the first time on or after the first intake of tapentadol PR during treatment, or adverse event started prior to the first dose and worsened in intensity after the first tapentadol PR intake during the treatment phase.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Tapentadol prolonged release

Reporting group description:

Subjects received doses between 100 to 250 mg tapentadol twice daily (50 and 100 mg tablets to be dispensed). A flexible titration to achieve sufficient pain relief to continue with effective analgesia for as long as the subject tolerates and wished to continue treatment was permited.

Serious adverse events	Tapentadol prolonged release		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 31 (45.16%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Malignant neoplasm progression			
subjects affected / exposed	9 / 31 (29.03%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 8		
Metastases to lung			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Cardiac failure	Additional description: Post-treatment adverse event leading to death 30 days after the last administration of tapentadol prolonged release. The subject did not have another serious adverse event.		
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Hypoxia	Additional description: Investigator indicated that the progression of the underlying malignancy (lung carcinoma) was associated with the hypoxia. Treatment emergent event leading to death.		
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Tapentadol prolonged release		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 31 (96.77%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to bone			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		
Malignant neoplasm progression			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	14		
Neoplasm progression			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Sinus tachycardia			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Nervous system disorders			
Dizziness			

subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Somnolence			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	6		
Lymphadenopathy			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Thrombocytopenia			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
General physical health deterioration			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	6		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Ascites			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	7		
Constipation			

subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	4 / 31 (12.90%) 4 9 / 31 (29.03%) 10		
Hepatobiliary disorders Hepatic function abnormal subjects affected / exposed occurrences (all)	 2 / 31 (6.45%) 4		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	 2 / 31 (6.45%) 2		
Musculoskeletal and connective tissue disorders Pathological fracture subjects affected / exposed occurrences (all)	 2 / 31 (6.45%) 2		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 2 / 31 (6.45%) 3 2 / 31 (6.45%) 2		
Metabolism and nutrition disorders Hypoalbuminaemia subjects affected / exposed occurrences (all)	 2 / 31 (6.45%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2011	Amendment 1: The protocol was updated with information relating to concomitant medication.
02 October 2012	Amendment 2: Changes in sponsor staff.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 May 2014	The trial was stopped for administrative reasons. Three years after trial initiation 2 participants were in the trial and to permit analysis and reporting the sponsor decided to terminate the trial.	-

Notes:

Limitations and caveats

None reported