Clinical trial results:
An open-label extension study for patients with severe chronic low back pain or severe chronic pain due to knee osteoarthritis who have completed any of the previous phase IIIb trials with tapentadol hydrochloride, KF5503/42, KF5503/44 or KF5503/45.

Summary

EudraCT number	2009-017470-20
Trial protocol	FR
Global end of trial date	23 April 2014

Results information

Result version number	v1 (current)
This version publication date	29 May 2016
First version publication date	29 May 2016

Trial information

Trial identification

Sponsor protocol code	GRT-CG5503-2009-02-FR

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Laboratoires Grünenthal
Sponsor organisation address	Immeuble Eureka - 19 rue Ernest Renan, Nanterre Cedex, France, CS90001 - 92024
Public contact	Grünenthal Clinical Trial Helpdesk, Grünenthal GmbH, +49 2415693223, clinical-trials@grunenthal.com
Scientific contact	Grünenthal Clinical Trial Helpdesk, Grünenthal GmbH, +49 2415693223, 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	18 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 April 2014
Global end of trial reached?	Yes
Global end of trial date	23 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal objective is to offer treatment with tapentadol hydrochloride to patients who have completed clinical trials KF5503/42, KF5503/44 or KF5503/45, and who could benefit from continued analgesic therapy with tapentadol.

Protection of trial subjects:

The trial was conducted according to ICH-GCP guidelines, the applicable French laws, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Regulatory and competent authorities were notified of the trial and relevant authorization was obtained.

Background therapy:

Three patients were included in this open-label extension. These patients were previously included in the KF 5503/44 trial: "An evaluation of the effectiveness and tolerability of tapentadol hydrochloride prolonged release, and tapentadol hydrochloride immediate release on demand, in patients with uncontrolled severe chronic nociceptive, mixed or neuropathic low back pain taking either WHO Step I or Step II analgesics or no regular analgesics".

Evidence for comparator: -

Actual start date of recruitment	23 June 2010
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	France: 3
Worldwide total number of subjects	3
EEA total number of subjects	3

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)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients who had completed one of the clinical trials: KF5503/42, KF5503/44 or KF5503/45 were eligible to continue in this trial. The trial consisted of 3 parts for subjects: an enrollment visit, an open-label treatment phase and a final visit. The enrollment visit coincided with the completion of the maintenance period of the previous trial.

Pre-assignment

Screening details:

French patients who benefited from tapentadol treatment and who had completed one of the clinical trials: KF5503/42, KF5503/44 or KF5503/45 were offered the opportunity to continue therapy on tapentadol. The first-patient-in was on 23 June 2010 and the last-patient-out was on the 23 April 2014.

Period 1

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

Blinding implementation details:

The primary objective was to offer treatment with Tapentadol hydrochloride to patients who had completed clinical trials KF5503/42, KF5503/44 or KF5503/45, and who could have benefited from continued analgesic therapy with Tapentadol.

Arms

Arm title	Tapentadol Prolonged Release

Arm description:

All patients maintained the same dose of tapentadol hydrochloride PR with which they have completed the preceding protocol, resulting from the dose titration and stabilization period.
The tapentadol hydrochloride PR dose may have been adjusted under certain circumstances, and following an established procedure. All dosage adjustments must have been made at a patient visit to the study centre.

Arm type	Experimental
Investigational medicinal product name	Tapentadol
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

During this open-label extension trial the minimal and maximal total daily doses of Tapentadol were from 300 to 600 mg.

Number of subjects in period 1	Tapentadol Prolonged Release
Started	3
Completed	2
Not completed	1
multiple reasons including pain intensity increase	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	3	3	
Age categorical Units: Subjects			
Adults (18-64 years)	3	3	
Age continuous Units: years			
arithmetic mean	44		
full range (min-max)	43 to 47	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	1	1	
Patient Global Impression of Change at Baseline			
In the Patient Global Impression of Change (PGIC) the subject indicated the perceived change over the treatment period in the previous trial. PGIC is a 7 point scale depicting a patient's rating of overall improvement. Patients rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse."			
Units: Subjects			
much improved	1	1	
very much improved	1	1	
minimally improved	1	1	
Height Units: meter			
arithmetic mean	1.69		
full range (min-max)	1.57 to 1.86	-	
Weight Units: kilogram(s)			
arithmetic mean	62		
full range (min-max)	55 to 73	-	
Body Mass Index (BMI) Units: kilogram(s)/square meter			
arithmetic mean	21.66		
full range (min-max)	21.1 to 22.31	-	
Pain Intensity at Baseline			
The recalled average pain intensity score on the NRS-3 was assessed using the 11-point NRS. This scale recalled the average pain intensity during the last 3 days. Pain intensity as evaluated by the 11-point NRS-3 scale at the visit. The patients have been asked to answer the following questions "Please rate your pain by circling the one number that best describes your current pain" wher 0 (is no pain) and 10 (indicated pain as bad as you can imagine).			
Units: unit(s)			
arithmetic mean	4.33		
full range (min-max)	0 to 7	-	
Systolic Blood Pressure			

Units: mmHg			
arithmetic mean	117.67		
full range (min-max)	111 to 124	-	
Diastolic Blood Pressure			
Units: mmHg			
arithmetic mean	65.33		
full range (min-max)	62 to 68	-	
Heart Rate			
Units: beat(s) per minute			
arithmetic mean	67.33		
full range (min-max)	62 to 74	-	

End points

End points reporting groups

Reporting group title	Tapentadol Prolonged Release

Reporting group description:

All patients maintained the same dose of tapentadol hydrochloride PR with which they have completed the preceding protocol, resulting from the dose titration and stabilization period.
The tapentadol hydrochloride PR dose may have been adjusted under certain circumstances, and following an established procedure. All dosage adjustments must have been made at a patient visit to the study centre.

Primary: Medical and ethical reasons

End point title	Medical and ethical reasons[1]

End point description:

Given the nature of the study, only a descriptive analysis was planned and no primary efficacy criterion or endpoint was defined.
The primary objective ot this open-label extension was to ofter, for medical and ethical reasons, a treatment with tapentadol hydrochloride to patients who had completed clinical trials KF5503/42, KF5503/44 or KF5503/45, and who could have benefited from continued analgesic therapy with tapentadol.

End point type	Primary

End point timeframe:

Baseline Visit (Day 1)

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: Because only 3 patients were enrolled, the analyses planned in the protocol could not be performed.

End point values	Tapentadol Prolonged Release			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: patient(s)				
number (not applicable)	3			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pain intensity NRS-3

End point title	Pain intensity NRS-3

End point description:

The recalled average pain intensity score on the NRS-3 was assessed using the 11-point NRS. This scale recalled the average pain intensity during the last 3 days. Pain intensity as evaluated by the 11-point NRS-3 scale at the visit. The patients have been asked to answer the following questions "Please rate your pain by circling the one number that best describes your current pain" wher 0 (is no pain) and 10 (indicated pain as bad as you can imagine).

End point type	Other pre-specified

End point timeframe:

Assessed at baseline, 4 weeks later and then at 8 weekly intervals up to 180 weeks after baseline.

End point values	Tapentadol Prolonged Release			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: unit(s)				
median (full range (min-max))				
Patient A	6 (4 to 7)			
Patient B	1 (0 to 7)			
Patient C	6 (4 to 8)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patient Global Impressions of Change (PGIC) at end of treatment

End point title	Patient Global Impressions of Change (PGIC) at end of treatment

End point description:

In the Patient Global Impression of Change (PGIC) the subject indicated the perceived change over the treatment period. PGIC is a 7 point scale depicting a patient's rating of overall improvement. Patients rate their change as “very much improved,” “much improved,” “minimally improved,” “no change,” “minimally worse,” “much worse,” or “very much worse.”

End point type	Other pre-specified

End point timeframe:

End of Study Visit (Week 20, 200 weeks and up to 208 weeks).

End point values	Tapentadol Prolonged Release			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: patient(s)				
Very much improved	1			
Much improved	1			
Minimally improved	1			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinician Global Impression of Change (CGIC) at end of treatment

End point title	Clinician Global Impression of Change (CGIC) at end of treatment

End point description:

The CGIC was chosen as a complementary assessment of efficacy. In the Clinician Global Impression of Change (CGIC) the investigator rates the perceived change for the patient over the treatment period. CGIC uses the 7 point scale depicting a clinician's rating of overall improvement. Patients rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse."

End point type	Other pre-specified

End point timeframe:

End of Study Visit (Week 20, 200 weeks and up to 208 weeks).

End point values	Tapentadol Prolonged Release			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: patients				
Very much improved	1			
Much improved	1			
Minimally improved	1			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Daily Dose of Tapentadol Prolonged Release

End point title	Mean Daily Dose of Tapentadol Prolonged Release

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline Visit (Day 1) to End of Study Visit (Week 20, 200 weeks and up to 208 weeks).

End point values	Tapentadol Prolonged Release			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: milligram(s)/24 hours				
arithmetic mean (full range (min-max))	441.76 (387.9 to 453.04)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Daily Dose of Tapentadol Immediate Release

End point title	Mean Daily Dose of Tapentadol Immediate Release

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline Visit (Day 1) to End of Study Visit (Week 20, 200 weeks and up to 208 weeks).

End point values	Tapentadol Prolonged Release			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: milligram(s)/24 hours				
arithmetic mean (full range (min-max))	3.99 (3.5 to 4.3)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Concomitant medications during the trial

End point title	Concomitant medications during the trial

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline Visit (Day 1) to End of Study Visit (Week 20, 200 weeks and up to 208 weeks).

End point values	Tapentadol Prolonged Release			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: patient(s)				
increase in venlafaxine dose	1			
alprazolam started	1			
single local lidocaine infiltration	1			
tramadol prolonged release	1			
tramadol-paracetamol combination	1			
naproxen	1			
paracetamol	1			
amoxicillin	1			
magnesium-vitamin B6	1			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Systolic Blood Pressure

End point title	Systolic Blood Pressure

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline Visit (Day 1) to End of Study Visit (Week 20, 200 weeks and up to 208 weeks).
Assessed at baseline, 4 weeks later and then at 8 weekly intervals up to 208 weeks after baseline.

End point values	Tapentadol Prolonged Release			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: mmHg				
arithmetic mean (standard deviation)				
Patient A	116.7 (± 7.7)			
Patient B	117.3 (± 3.9)			
Patient C	120.1 (± 4.7)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Diastolic blood pressure

End point title	Diastolic blood pressure

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline Visit (Day 1) to End of Study Visit (Week 20, 200 weeks and up to 208 weeks).
Assessed at baseline, 4 weeks later and then at 8 weekly intervals up to 208 weeks after baseline.

End point values	Tapentadol Prolonged Release			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: mmHg				
arithmetic mean (standard deviation)				
Patient A	71 (± 8.6)			
Patient B	66.4 (± 3.6)			
Patient C	66.5 (± 4.6)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Heart Rate

End point title	Heart Rate

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline Visit (Day 1) to End of Study Visit (Week 20, 200 weeks and up to 208 weeks).
Assessed at baseline, 4 weeks later and then at 8 weekly intervals up to 208 weeks after baseline.

End point values	Tapentadol Prolonged Release			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: beat(s) per minute				
arithmetic mean (standard deviation)				
Patient A	81.3 (± 15.3)			
Patient B	65.3 (± 3.7)			
Patient C	63.6 (± 3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: up to 208 weeks after baseline visit	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Tapentadol Prolonged Release

Reporting group description:

All patients maintained the same dose of tapentadol hydrochloride prolonged release (PR) with which they completed the preceding protocol, resulting from the dose titration and stabilization period. The tapentadol hydrochloride PR dose may have been adjusted under certain circumstances, and following an established procedure. All dosage adjustments must have been made at a patient visit to the study centre.

Serious adverse events	Tapentadol Prolonged Release		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Tapentadol Prolonged Release		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Epicondylitis subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Infections and infestations Pharyngitis subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2012	There was one amendment to the original protocol (dated 21 Dec 2009). Apart from minor editorial corrections, the following changes were implemented by the amendment 01 (dated 9 Mar 2012): new address of the sponsor, updated study timelines, changes in the sponsor staff and improvement of the clarity and the consistency within the relevant protocol sections.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported