ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 03/24/2015

A Study to Evaluate Tapentadol (CG5503) in the Treatment of Chronic Tumor-Related Pain Compared With Placebo and Morphine

This study has been completed.

Sponsor:	Grünenthal GmbH
Collaborators:	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Information provided by (Responsible Party):	Grünenthal GmbH
ClinicalTrials.gov Identifier:	NCT00472303

Purpose

The purpose of this study will be to determine whether tapentadol (CG5503) is effective and safe in the treatment of chronic tumor related pain compared to placebo. In addition tapentadol (CG5503) will also be compared to morphine controlled release, also referred to as slow release (SR).

*Tapentadol prolonged-release (PR) is the term used in the European Union and is referred to as extended release (ER) in the United States.

Condition	Intervention	Phase
Tumor Pain	Drug: Tapentadol Extended Release Drug: Matching Placebo after Tapentadol in the Titration Phase. Drug: Morphine Sulphate Controlled Release	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Randomized, Efficacy Study
Official Title: A Randomized Withdrawal, Active- and Placebo-controlled, Double-blind, Multi-center Phase III Trial Assessing Safety and Efficacy of Oral CG5503 (Tapentadol) PR* in Subjects With Moderate to Severe Chronic Malignant Tumor-related Pain

Further study details as provided by Grünenthal GmbH:

Primary Outcome Measure:

- Number of Participants Scored as Responder in Maintenance Phase. [Time Frame: Day 18 through Day 43 (End of Maintenance Phase)] [Designated as safety issue: No]

  A "responder" is a participant in the study that: 1. completed 28 days of the maintenance phase 2. had a numeric rating scale score below 5 on the 11 point scale (where 0 indicates no pain and 10 indicates worst possible pain. This twice daily current pain score was averaged over Day 18 to Day 43. 3. did not use more than 20 mg of rescue medication per day on average in the 28 day maintenance period (from Day 18 to Day 43). A participant that met all 3 of the above-mentioned criteria is counted as a responder, in other words the participant benefited from the assigned drug treatment. A participant that failed to meet only 1 of the 3 criteria is not counted as a responder.

Secondary Outcome Measures:

- Average Daily Pain Intensity Scores, Averaged Per Week by Treatment, During the Titration Phase in the Tapentadol Treatment Arm. [Time Frame: Day 1 through Day 14 (End of Titration Phase)] [Designated as safety issue: No]

  Participants were asked to record their "average pain over the last 24 hours" pain intensity each evening. Average pain scores are the averages of all scores recorded during each week. 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 Daily Pain Intensity Scores, Averaged Per Week by Treatment, During the Titration Phase in the Morphine Treatment Arm. [Time Frame: Day 1 through Day 14 (End of Titration Phase)] [Designated as safety issue: No]

  Participants were asked to record their "average pain over the last 24 hours" pain intensity each evening. Average pain scores are the averages of all scores recorded during each week. 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 Daily Pain Intensity Scores, Averaged Per Week by Treatment, During the Maintenance Phase. [Time Frame: Day 18 through Day 43 (End of Maintenance Phase)] [Designated as safety issue: No]

  Participants were asked to record their "average pain over the last 24 hours" pain intensity each evening. Average pain scores are the averages of all scores recorded during each week. 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".
- Current Pain Intensity Scores, Averaged Per Week, During the Titration Phase in the Tapentadol Arm. [Time Frame: Day 1 through Day 14 (End of Titration Phase)] [Designated as safety issue: No]

  Participants were asked to record their current pain intensity in the morning and evening. Average pain scores are the averages of all scores recorded during each week. 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".
- Current Pain Intensity Scores, Averaged Per Week, During the Titration Phase in the Morphine Arm. [Time Frame: Day 1 through Day 14 (End of Titration Phase)] [Designated as safety issue: No]

  Participants were asked to record their current pain intensity in the morning and evening. Average pain scores are the averages of all scores recorded during the during each week. 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".
- Current Pain Intensity Scores, Averaged Per Week by Treatment, During the Maintenance Phase. [Time Frame: Day 15 through Day 43 (End of Maintenance Phase)] [Designated as safety issue: No]

  Participants were asked to record their current pain intensity in the morning and evening. Average pain scores are the averages of all scores recorded during the 3 days prior to re-randomization or during each week. 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".
- Use of Rescue Medication in the Titration Phase. [Time Frame: Day 1 through Day 14 (End of Titration Phase)] [Designated as safety issue: No]

  The number of participants using rescue medication morphine sulfate immediate release 10 mg tablets in the titration phase were counted. This data was captured in an electronic diary. During the trial, morphine immediate release 10 mg was allowed as required without a maximum dose defined.

However, participants were only re-randomized if their mean consumption of rescue medication was less or equal to 2 doses (20 mg) per day during the last 3 days of the titration phase).

- Number of Participants Using Immediate Release Morphine Rescue Medication in the Maintenance Phase [Time Frame: Day 15 through Day 43 (End of Maintenance Phase)] [Designated as safety issue: No]

  Participants were issued morphine 10 mg immediate release medication. The number of participants using rescue medication morphine sulfate immediate release 10 mg tablets in the maintenance phase were counted. This use of morphine immediate release was captured in each participant's electronic diary.
- The Average Mean Total Daily Dose of Rescue Medication. [Time Frame: Day 1 (Start of Titration Phase) through Day 43 (End of Maintenance Phase)] [Designated as safety issue: No]

  Mean total daily dose of rescue medication morphine sulphate immediate release tablets in milligrams per day (mg/day).
- Changes in the Short Form 36® Health Survey (SF-36®) During the Titration Phase. [Time Frame: Day 1 (Start of Titration); Day 14 (End of Titration Phase)] [Designated as safety issue: No]

  The Short Form 36 (SF-36) includes several brief questions on 8 aspects, (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health) that a participant was asked to score over the last week. Low scores on the Physical Component Summary measure indicate limitations in physical functioning, e.g. a high degree of bodily pain and physical limitations etc. For the Mental Component Summary measure, a low score is indicative of frequent psychological distress, social and role disability due to emotional problems etc. The theoretical range for the physical component score is 12.3279 to 59.6503. The theoretical range for the mental component score is 13.5313 to 59.6503. Positive values for changes in the component scores indicate an improvement.
- Changes in the Short Form 36® Health Survey (SF-36®) During the Maintenance Phase. [Time Frame: Day 15 (Start of Maintenance); Day 43 (End of Maintenance Phase)] [Designated as safety issue: No]

  The Short Form 36 (SF-36) includes several brief questions on 8 aspects, (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health) that a participant was asked to score over the last week. Low scores on the Physical Component Summary measure indicate limitations in physical functioning, e.g. a high degree of bodily pain and physical limitations etc. For the Mental Component Summary measure, a low score is indicative of frequent psychological distress, social and role disability due to emotional problems etc. The theoretical range for the physical component score is 12.3279 to 59.6503. The theoretical range for the mental component score is 13.5313 to 59.6503. Positive values for changes in the component scores indicate an improvement.
- Change in the EuroQoL (EQ-5D) Health Status Index (United Kingdom Time Trade-off Value Set) Change From Start of Titration to Endpoint Titration. [Time Frame: Day 1 (Start of Titration); Day 14 (End of Titration Phase)] [Designated as safety issue: No]

  The participant scores the EuroQol-5D. The EuroQoL-5D is a five dimensional health state classification. Each dimension is assessed on a 3-point ordinal scale (1 = no problems, 2 = some problems, 3 = extreme problems). The responses to the five EQ-5D dimensions are scored using a utility-weighted algorithm to derive an EQ-5D health status index score between 0 to 1, with 1.00 indicating "full health" and 0 representing dead. A positive change in the mean indicates that during this phase the health status improved. A positive change indicates an improvement in health. The minimal important difference is 0.074 (range -0.011 to 0.140).
- Health Related Quality of Life: EuroQol-5D Health State Visual Analog Scale (VAS) Titration Phase. [Time Frame: Day 1 (Start of Titration); Day 14 (End of Titration Phase)] [Designated as safety issue: No]

  EuroQoL-5D Health State Visual Analog Scale (VAS) is a participant rated questionnaire to assess health-related quality of life in terms of a single index value. The VAS component rates current health state on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state); higher scores indicate better health. The values indicated represent the change from Day 1, a positive value indicates an improvement since the start of treatment.
- Change in the EuroQoL (EQ-5D) Health Status Index (United Kingdom Time Trade-off Value Set) Over Time in the Maintenance Phase for Tapentadol and the Placebo Randomized Withdrawal Treatment Arms. [Time Frame: Day 15 (Start of Maintenance); Day 43 (End of Maintenance Phase)] [Designated as safety issue: No]

  The participant scores the EuroQol-5D. The EuroQoL-5D is a five dimensional health state classification. Each dimension is assessed on a 3-point ordinal scale (1 = no problems, 2 = some problems, 3 = extreme problems). The responses to the five EQ-5D dimensions are scored using a utility-weighted algorithm to derive an EQ-5D health status index score between 0 to 1, with 1.00 indicating "full health" and 0 representing dead. A negative

change in the mean indicates a worsening in health status since the beginning of the maintenance phase. A positive change indicates an improvement in health. The minimal important difference in the Health Status Index is 0.074 (range -0.011 to 0.140).

- Changes in Health Related Quality of Life: EuroQol-5D Health State Visual Analog Scale (VAS) Maintenance Phase. [Time Frame: Day 15 (Start of Maintenance); Day 43 (End of Maintenance Phase)] [Designated as safety issue: No]

  EuroQoL-5D Health State Visual Analog Scale (VAS) is a participant rated questionnaire to assess health-related quality of life in terms of a single index value. The VAS component rates current health state on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state); higher scores indicate a better health state. The values indicated represent the change from Day 15, a negative mean value indicates a worsening of health-related quality of life since the start of the maintenance phase.
- Patient Global Impression of Change [Time Frame: Day 43 (End of Maintenance Phase)] [Designated as safety issue: No]

  In the Patient Global Impression of Change (PGIC) the participant is asked "Since I began study treatment, my overall status is". The participant is asked to circle one of seven categories. Scores range from very much improved to very much worse. The question was asked at the end of the maintenance phase with reference to the start of the maintenance phase where the participant continued at the dose that was effective at the end of the Titration Phase.
- Quality of Sleep (Sleep Questionnaire) in the Titration Phase. [Time Frame: Day 1 (Start of Titration); Day 14 (end of Titration Phase)] [Designated as safety issue: No]

  Participants were asked the following question: "Please rate the overall quality of your sleep last night?" The quality of sleep from the start of the titration phase to the end of the titration phase was measured. The participant could choose one of the following options: Excellent, good, fair and poor.
- Quality of Sleep (Sleep Questionnaire) During the Maintenance Phase of the Trial. [Time Frame: Day 15 (Start of Maintenance); Day 43 (End of Maintenance Phase)] [Designated as safety issue: No]

  Participants were asked the following question: "Please rate the overall quality of your sleep last night?" The quality of sleep from the start of maintenance to the completion of treatment is reported. The participant could choose one of the following options: Excellent, good, fair and poor.
- Clinical Opioid Withdrawal Scale (COWS) at the End of the Titration Phase. [Time Frame: Day 14 (End of Titration Phase)] [Designated as safety issue: Yes]

  This instrument was developed by the National Institute on Drug Abuse. The physical components of withdrawal are primarily evaluated and based on questions and clinical observations. The possible opioid withdrawal effects are assessed using the Clinical Opioid Withdrawal Score (COWS). The COWS is a clinician rated 11-item scale that primarily evaluates the physical components of opioid withdrawal and is based on questions and clinical observations. Responses are rated on a Likert-type scale ranging from 0 to 4 or 5 depending on the item. The total COWS score is the sum of all individual items. The following withdrawal categories are based on the total COWS score: - None: total score below 5; - Mild: total score from 5 to 12; - Moderate: total score 13 to 24; - Moderately Severe: total score 25 to 36; - Severe: total score above 36. The investigator completes the COWS after participants discontinued trial medication 2 to less than 5 days after last intake of trial medication.
- Clinical Opioid Withdrawal Score (COWS) at the End of the Maintenance Phase. [Time Frame: Day 43 (End of Maintenance Phase)] [Designated as safety issue: Yes]

  This instrument was developed by the National Institute on Drug Abuse. The physical components of withdrawal are primarily evaluated and based on questions and clinical observations. The possible opioid withdrawal effects are assessed using the Clinical Opioid Withdrawal Score (COWS). The COWS is a clinician rated 11-item scale that primarily evaluates the physical components of opioid withdrawal and is based on questions and clinical observations. Responses are rated on a Likert-type scale ranging from 0 to 4 or 5 depending on the item. The total COWS score is the sum of all individual items. The following withdrawal categories are based on the total COWS score: - None: total score below 5; - Mild: total score from 5 to 12; - Moderate: total score 13 to 24; - Moderately Severe: total score 25 to 36; - Severe: total score above 36. The investigator completes the COWS after participants discontinued trial medication 2 to less than 5 days after last intake of trial medication.
- Change in the Patient Assessment of Constipation Symptoms (PAC-SYM) During the Titration Phase [Time Frame: Day 1 (Start of Titration); Day 14 (End of Titration Phase)] [Designated as safety issue: Yes]

  The Constipation Assessment (PAC-SYM) is a 12-item self-report questionnaire that assesses the severity of symptoms of constipation. Participants are asked "How severe have each of these symptoms been in the last two weeks?" e.g. "Pain in your stomach". There are 3 subscales: 4 questions on Abdominal symptoms, 3 questions on rectal symptoms and 5 questions on stool symptoms. Responses are rated on a 5-point Likert Scale ranging from 0 (absence of symptom) to 4 (very severe symptoms). The changes in overall mean and in each of the mean sub-scores vary theoretically from -4 to +4

(where a change of +4 would indicate a change from not present to very severe symptom). If the changes in the overall or subscale mean scores are positive then there is a worsening in symptoms associated with constipation from the start to the end of the titration phase.

- Change in the Patient Assessment of Constipation Symptoms (PAC-SYM) During the Maintenance Phase [Time Frame: Day 15 (Start of Maintenance); Day 43 (End of Maintenance Phase)] [Designated as safety issue: Yes]

  The Constipation Assessment (PAC-SYM) is a 12-item self-report questionnaire that assesses the severity of symptoms of constipation. Participants are asked "How severe have each of these symptoms been in the last two weeks?" e.g. "Pain in your stomach". There are 3 subscales: 4 questions on Abdominal symptoms, 3 questions on rectal symptoms and 5 questions on stool symptoms. Responses are rated on a 5-point Likert Scale ranging from 0 (absence of symptom) to 4 (very severe symptoms). The changes in overall mean and in each of the mean sub-scores vary theoretically from -4 to +4 (where a change of +4 would indicate a change from not present to very severe symptom). If the changes in the overall or subscale mean scores are positive then there is a worsening in symptoms associated with constipation from the start to the end of the maintenance phase. A negative mean change indicates an improvement.

Enrollment: 622
Study Start Date: July 2007
Primary Completion Date: June 2012
Study Completion Date: June 2012

Arms	Assigned Interventions
Placebo Comparator: Matching Placebo after Tapentadol in Titration Phase Oral Tapentadol 100 mg to 250 mg twice daily. Participants randomized to placebo in the maintenance phase received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off the tapentadol dose they had received in the Titration Phase. From the 4th day (Day 18) all participants received matching placebo in the maintenance (i.e. randomized withdrawal) phase.	Drug: Tapentadol Extended Release Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. Titration phase: Starting at 100 mg, increasing at a minimum of 3 day intervals by 50 mg, with a maximum dose of 250 mg. Other Names: Palexia Nucynta Yantil Drug: Matching Placebo after Tapentadol in the Titration Phase. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. In the maintenance phase only to participants that were randomized to tapentadol in the titration phase.
Active Comparator: Morphine Controlled Release Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. Maintenance phase: continuing on dose level established in titration phase.	Drug: Morphine Sulphate Controlled Release Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. Titration phase: Starting at 40 mg, increasing at a minimum of 3 days intervals by 20 mg, with a maximum dose of 100 mg. Maintenance phase: continuing on dose level established in titration phase.

Arms	Assigned Interventions
	Other Names: MST® CONTINUS®
Experimental: Tapentadol Prolonged Release Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.	Drug: Tapentadol Extended Release Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. Titration phase: Starting at 100 mg, increasing at a minimum of 3 day intervals by 50 mg, with a maximum dose of 250 mg. Other Names: Palexia Nucynta Yantil

Detailed Description:

Normally chronic tumor related pain is controlled when participants receive repeated doses of opioid analgesics. However, opioid therapy is commonly associated with side effects such as nausea, vomiting, sedation, constipation, addiction, tolerance, and respiratory depression. Tapentadol (CG5503), a newly synthesized drug with an prolonged release (PR) formulation, also acts as a centrally acting pain reliever but has 2 mechanisms of action. The aim of this trial is to investigate the effectiveness (level of pain control) and safety (side effects) of tapentadol (CG5503) PR compared with no drug (placebo) and corresponding dose of morphine (an opioid commonly used to treat tumor related pain). This trial is a randomized, double-blind (neither investigator nor patient will know which treatment was received), active- and placebo-controlled, parallel-group, randomized withdrawal design, multicenter trial.

The trial includes a 2 week titration phase starting with either 40 mg morphine (PR) bid (bid = twice daily dosing, one dose in the morning and one dose in the evening) or 100 mg tapentadol (CG5503) PR bid. Based on effectiveness and side effects subjects can up-titrate in steps of 50 mg tapentadol (CG5503 PR) to a maximal dose of 250 mg tapentadol (CG5503) PR bid or 100 mg morphine PR bid. If participants meet the stabilisation criteria at the end of the titration phase they will be re-randomized to either placebo or active treatment and will continue 4 weeks at the last dose level in the maintenance phase. Only participants on tapentadol in the titration phase will be re-randomized to either matching placebo or to tapentadol. To maintain the blinding nature of the trial participants in the morphine arm during the titration phase will also be re-randomized however they will all remain on morphine controlled release in the maintenance phase. Placebo to match tapentadol tablets, as well as placebo to match morphine capsules, will be used to mask the treatment allocation.

Participants will be issued with an electronic diary (eDiary) to capture Numeric Rating Scale (NRS) pain intensities.

Assessments of pain relief include the pain intensity numeric rating scale (NRS) and patient global impression of change (PGIC). Safety evaluations include monitoring of adverse events, physical examinations, clinical laboratory tests and electrocardiograms. Venous blood samples will be collected for the determination of serum concentrations of tapentadol (CG5503).

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria

- Male and non-pregnant, non-lactating female subjects.
- Of at least 18 years of age with chronic malignant tumor-related pain with a mean pain intensity (NRS) of 5 points or higher.
- Subjects who are opioid-naïve or pretreated with an equianalgesic dose range equivalent of up to 160 mg oral morphine per day and are dissatisfied with prior treatment.
- Women must be postmenopausal, surgically sterile, or practicing or agree to practice an effective method of birth control throughout the trial.
- Expected course of the disease and the pain that would permit compliance with the trial protocol over the entire trial period.

Exclusion Criteria

Key Exclusion Criteria:

- Subjects will be excluded from the study if they have a history of seizure disorder or epilepsy;
- known history and/or presence of cerebral tumor or cerebral metastases.
- history of alcohol or drug abuse;
- uncontrolled hypertension,
- clinical laboratory values reflecting severe renal insufficiency,
- moderate or severe hepatic impairment,
- hepatitis B or C, HIV,
- inadequate bone marrow reserve
- currently treated with radiotherapy,
- pain-inducing chemotherapy,
- anti-parkinsonian drugs, neuroleptics, monoamine oxidase inhibitors, serotonin norepinephrine reuptake inhibitor (SNRI) or any other analgesic therapy than investigational medication or rescue medication during the trial.
- selective serotonin reuptake inhibitor (SSRI) treatments are allowed if taken for at least 30 days before the screening period of the study at an unchanged dose.

Contacts and Locations

Locations

Austria

Site 043004
Klagenfurt, Austria, 9020

Site 043007
Oberpullendorf, Austria, 7350

Site 043008
Salzburg, Austria, 5020

Site 043001
Vienna, Austria, 1090

Site 043002
Vienna, Austria, 1020

Site 043005
Vienna, Austria, 1100

Bulgaria

Site 359013
Gabrovo, Bulgaria, 5300
Site 359011
Pleven, Bulgaria, 5800
Site 359014
Plovdiv, Bulgaria, 4004
Site 359004
Shoumen, Bulgaria, 9700
Site 359008
Sofia, Bulgaria, 1784
Site 359006
Sofia, Bulgaria, 1233
Site 359012
Varna, Bulgaria, 9003
Croatia
Site 385007
Osijek, Croatia, 31000
Site 385005
Rijeka, Croatia, 51000
Site 385001
Slavonski Brod, Croatia, 35000
Site 385004
Varazdin, Croatia, 42000
Site 385006
Zabok, Croatia, 49210
Site 385002
Zagreb, Croatia, 10000
Site 385003
Zagreb, Croatia, 10000
Czech Republic
Site 420005
Brno, Czech Republic, 62500
Site 420002
Ceske Budejovice, Czech Republic, 37087
Site 420006
Hradec Kralove, Czech Republic, 50005
Site 420007
Liberec, Czech Republic, 46063
Site 420008
Olomouc, Czech Republic, 77520
Site 420001
Pilsen, Czech Republic, 30460
Site 420004
Prague, Czech Republic, 18181
Site 420003

Prague, Czech Republic, 12808

France

Site 033101

Tarbes, France, 65000

Germany

Site 049009

Berlin, Germany, 12627

Site 049016

Berlin, Germany, 14165

Site 049017

Berlin, Germany, 13125

Site 049022

Berlin, Germany, 14089

Site 049018

Blankenhain, Germany, 99444

Site 049014

Essen, Germany, 45122

Site 049023

Hamburg, Germany, 22767

Site 049024

Hamburg, Germany, 22081

Site 049001

Hamburg, Germany, 20253

Site 049003

Herrsching, Germany, 82211

Site 049005

Hildesheim, Germany, 31134

Site 049012

Köln, Germany, 50996

Site 049007

Loewenstein, Germany, 74245

Site 049020

Potsdam, Germany, 14467

Site 049006

Waldkirch, Germany, 79183

Site 049002

Wiesbaden, Germany, 65185

Site 049021

Wiesbaden, Germany, 65189

Hungary

Site 036001

Debrecen, Hungary, 4043

Site 036005

Komárom, Hungary, 2900

Site 036003

Mátraháza, Hungary, 3233
Site 036002
Nyiregyhaza, Hungary, 4412
Site 036010
Szekszard, Hungary, 7100
Site 036009
Székesfehérvár, Hungary, 8000
Site 036006
Székesfehérvár, Hungary, 8000
Site 036004
Zalaegerszeg, Hungary, 8900
Italy
Site 039002
Modena, Italy, 41100
Site 039001
Napoli, Italy, 80131
Moldova, Republic of
Site 373001
Chisinau, Moldova, Republic of, 2025
Site 373002
Chisinau, Moldova, Republic of, 2025
Netherlands
Site 031002
Amsterdam, Netherlands, 1091
Site 031004
Amsterdam, Netherlands, 1105
Site 031003
Nijmegen, Netherlands, 2565
Site 031001
Stadskanaal, Netherlands, 9501
Poland
Site 048008
Bielsko-Biała, Poland, 43300
Site 048004
Bydgoszcz, Poland, 85796
Site 048005
Gdanks, Poland, 80286
Site 048006
Gdansk, Poland, 80952
Site 048007
Poznan, Poland, 60355
Site 048002
Poznan, Poland, 61866
Site 048003
Szczecin, Poland, 70421

Site 048001
Warszawa, Poland, 02781
Romania
Site 040006
Brasov, Romania, 500074
Site 040002
Bucharest, Romania, 022328
Site 040003
Bucharest, Romania, 022328
Site 040004
Bucharest, Romania, 022328
Site 040005
Cluj-Napoca, Romania, 400015
Site 040001
Iasi, Romania, 700106
Site 040007
Timisoara, Romania, 300239
Russian Federation
Site 007010
Arkhangels, Russian Federation, 163045
Site 007003
Moscow, Russian Federation, 125284
Site 007002
Moscow, Russian Federation, 127018
Site 007007
Nizhniy Novgorod, Russian Federation, 603140
Site 007012
Vladikavkaz, Russian Federation, 362007
Site 007005
Yaroslavl, Russian Federation, 150054
Serbia
Site 381003
Belgrade, Serbia, 11000
Site 381004
Belgrade, Serbia, 11000
Site 381005
Belgrade, Serbia, 11000
Site 381002
Nis, Serbia, 18000
Site 381001
Sremska Kamenica, Serbia, 21204
Slovakia
Site 421005
Banska Bystrica, Slovakia, 97517
Site 421001

Kosice, Slovakia, 04191
Site 421004
Zilina, Slovakia, 01207
Spain
Site 034005
Barcelona, Spain, 08221
Site 034008
Barcelona, Spain, 08243
Site 034009
Barcelona, Spain, 08208
Site 034011
Granada, Spain, 18014
Site 034006
Mahon Menorca, Spain, 07703
Site 034007
Palma de Mallorca, Spain, 07014
Site 034012
Pamplona, Spain, 31008
Site 034004
Sevilla, Spain, 1013
Site 034002
Valencia, Spain, 46014
Site 034010
Sagunto, Valencia, Spain, 46520
Sweden
Site 046001
Stockholm, Sweden, 17176
Site 046002
Västeras, Sweden, 72189
Switzerland
Site 041001
Bruderholz, Switzerland, 4101

Investigators

Principal Investigator:	Hans Georg Kress, Dr.	Clinic of Anaesthesiology and Pain Management, AKH Vienna

More Information

Results Publications:

Kress HG, Koch ED, Kosturski H, Steup A, Karcher K, Lange B, Dogan C, Etropolski MS, Eerdekens M. Tapentadol prolonged release for managing moderate to severe, chronic malignant tumor-related pain. Pain Physician. 2014 Jul-Aug;17(4):329-43.

Responsible Party: Grünenthal GmbH

Study ID Numbers:	761101 2006-004997-28 [EudraCT Number] KF5503/15 [Grünenthal]
Health Authority:	Bulgaria: Bulgarian Drug Agency Czech Republic: State Institute for Drug Control Hungary: National Institute of Pharmacy Poland: The Central Register of Clinical Trials Romania: National Medicines Agency Russia: Ministry of Health of the Russian Federation Serbia and Montenegro: Agency for Drugs and Medicinal Devices Slovakia: State Institute for Drug Control Germany: Federal Institute for Drugs and Medical Devices Austria: Agency for Health and Food Safety Switzerland: Swissmedic Italy: The Italian Medicines Agency Croatia: Ministry of Health and Social Care Spain: Agencia Española de Medicamentos y Productos Sanitarios Sweden: Medical Products Agency Netherlands: The Central Committee on Research Involving Human Subjects (CCMO) France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis) Moldova: Ministry of Health

Study Results

Participant Flow

Recruitment Details	The trial started on 13 Jun 2007 with the enrollment of the first participant and was completed on 04 Jun 2012 with the last follow-up examination. 622 participants signed informed consent. 505 participants were randomized and 504 had at least one dose of trial medication. 496 participants were part of the safety analysis set.
Pre-Assignment Details	One site was excluded from all analysis sets (efficacy and safety) due to GCP non-compliance. Thus 8 participants who were randomized and treated are not reported in the tables below. The participants in the tapentadol titration phase were re-randomized to tapentadol or placebo in the maintenance phase.

Reporting Groups

	Description
Tapentadol Prolonged Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.
Matching Placebo After Tapentadol in Titration Phase	Oral Tapentadol 100 mg to 250 mg twice daily. Participants randomized to placebo received 100 mg tapentadol prolonged release (PR) twice daily for 3 days to taper them off the tapentadol dose they had received in the Titration Phase. From the 4th day (Day 18) all participants received matching placebo in the maintenance (i.e. randomized withdrawal) phase.

Titration Phase

	Tapentadol Prolonged Release	Morphine Controlled Release	Matching Placebo After Tapentadol in Titration Phase
Started	338	158	0 [1]
Completed	279	129	0
Not Completed	59	29	0
Adverse Event	22	12	0
Death	4	2	0
Lack of Efficacy	10	0	0
Withdrawal by Subject	16	13	0
Trial Medication non-compliant	4	1	0
not specified	3	1	0

[1] All participants in the titration phase were in the tapentadol arm during the titration phase.

Discontinuations After Titration Phase

	Tapentadol Prolonged Release	Morphine Controlled Release	Matching Placebo After Tapentadol in Titration Phase
Started	279	129	0
Completed	218 [1]	109 [1]	0
Not Completed	61	20	0
Adverse Event	6	0	0

	Tapentadol Prolonged Release	Morphine Controlled Release	Matching Placebo After Tapentadol in Titration Phase
Lack of Efficacy	48	17	0
Withdrawal by Subject	2	2	0
Trial Medication non-compliant	0	1	0
not specified	5	0	0

[1] Participants meeting stabilization criteria on days 13-15 in the titration phase were re-randomized.

Maintenance Phase

	Tapentadol Prolonged Release	Morphine Controlled Release	Matching Placebo After Tapentadol in Titration Phase
Started	106 [1]	109	112 [2]
Completed	89	93	95
Not Completed	17	16	17
Adverse Event	5	6	6
Death	3	0	2
Lack of Efficacy	2	2	4
Withdrawal by Subject	6	7	3
Trial medication non-compliant	0	0	1
Resolution of pain	0	0	1
not specified	1	1	0

[1] 106 of 218 participants in the tapentadol titration arm were re-randomized and treated.
[2] 112 of 218 participants in the tapentadol titration arm were re-randomized and treated.

Baseline Characteristics

Analysis Population Description

Titration Phase:

Safety Analysis Set (N = 496) Full Analysis Set (N = 492)

Maintenance Phase:

Safety Analysis Set (N = 327) Full Analysis Set (N = 325)

Note:

One site was excluded from all analysis sets (efficacy and safety) due to GCP non-compliance. Thus 8 participants who were randomized and treated are not reported in the tables below.

Reporting Groups

	Description
Tapentadol Prolonged Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.

Baseline Measures

	Tapentadol Prolonged Release	Morphine Controlled Release	Total
Number of Participants	338	158	496
Age, Categorical [units: participants]			
<=18 years	0	0	0
Between 18 and 65 years	224	102	326
>=65 years	114	56	170
Age, Continuous [units: years] Mean (Standard Deviation)	59.8 (10.39)	61.5 (10.21)	60.4 (10.35)
Gender, Male/Female [units: participants]			
Female	150	75	225
Male	188	83	271
Region of Enrollment [units: participants]			
Austria	5	3	8
Bulgaria	21	13	34
Croatia	27	11	38
Czech Republic	12	3	15
France	1	0	1

	Tapentadol Prolonged Release	Morphine Controlled Release	Total
Germany	33	14	47
Hungary	40	21	61
Italy	1	0	1
Moldova, Republic of	14	5	19
Poland	24	13	37
Romania	47	21	68
Russian Federation	51	26	77
Serbia	37	19	56
Slovakia	4	1	5
Spain	18	6	24
Sweden	3	2	5

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Participants Scored as Responder in Maintenance Phase.
Measure Description	A "responder" is a participant in the study that: 1. completed 28 days of the maintenance phase 2. had a numeric rating scale score below 5 on the 11 point scale (where 0 indicates no pain and 10 indicates worst possible pain. This twice daily current pain score was averaged over Day 18 to Day 43. 3. did not use more than 20 mg of rescue medication per day on average in the 28 day maintenance period (from Day 18 to Day 43). A participant that met all 3 of the above-mentioned criteria is counted as a responder, in other words the participant benefited from the assigned drug treatment. A participant that failed to meet only 1 of the 3 criteria is not counted as a responder.
Time Frame	Day 18 through Day 43 (End of Maintenance Phase)
Safety Issue?	No

Analysis Population Description

Full Analysis Set (Maintenance Phase).

Reporting Groups

	Description
Tapentadol Prolonged Release (Maintenance Phase)	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.
Morphine Controlled Release (Maintenance Phase)	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.
Matching Placebo After Tapentadol in Titration Phase	Oral Tapentadol 100 mg to 250 mg twice daily. Participants randomized to placebo in the maintenance phase received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off the tapentadol dose they had received in the Titration Phase. From the 4th day (Day 18) all participants received matching placebo in the maintenance (i.e. randomized withdrawal) phase.

Measured Values

	Tapentadol Prolonged Release (Maintenance Phase)	Morphine Controlled Release (Maintenance Phase)	Matching Placebo After Tapentadol in Titration Phase
Number of Participants Analyzed	105	109	111
Number of Participants Scored as Responder in Maintenance Phase. [units: participants]	65	75	55

2. Secondary Outcome Measure:

Measure Title	Average Daily Pain Intensity Scores, Averaged Per Week by Treatment, During the Titration Phase in the Tapentadol Treatment Arm.
Measure Description	Participants were asked to record their "average pain over the last 24 hours" pain intensity each evening. Average pain scores are the averages of all scores recorded during each week. 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".
Time Frame	Day 1 through Day 14 (End of Titration Phase)
Safety Issue?	No

Analysis Population Description

Full Analysis Set (Titration Period), observed.

Reporting Groups

	Description
Tapentadol Prolonged Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.

Measured Values

	Tapentadol Prolonged Release
Number of Participants Analyzed	329
Average Daily Pain Intensity Scores, Averaged Per Week by Treatment, During the Titration Phase in the Tapentadol Treatment Arm. [units: units on a scale] Mean (Standard Deviation)	
Prior to start of the Titration Phase (N = 282)	6.315 (1.4435)
End of Week 1 of the Titration Phase (N = 329)	5.324 (1.7476)
End of Week 2 of the Titration Phase (N = 295)	4.021 (1.6872)

3. Secondary Outcome Measure:

Measure Title	Average Daily Pain Intensity Scores, Averaged Per Week by Treatment, During the Titration Phase in the Morphine Treatment Arm.
Measure Description	Participants were asked to record their "average pain over the last 24 hours" pain intensity each evening. Average pain scores are the averages of all scores recorded during each week. 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".
Time Frame	Day 1 through Day 14 (End of Titration Phase)
Safety Issue?	No

Analysis Population Description

Full Analysis Set (Titration Period), observed.

Reporting Groups

	Description
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.

Measured Values

	Morphine Controlled Release
Number of Participants Analyzed	156
Average Daily Pain Intensity Scores, Averaged Per Week by Treatment, During the Titration Phase in the Morphine Treatment Arm. [units: units on a scale] Mean (Standard Deviation)	
Prior to start of the Titration Phase (N = 135)	6.162 (1.5693)
End of Week 1 of the Titration Phase (N = 156)	4.906 (1.9039)
End of Week 2 of the Titration Phase (N = 135)	3.669 (1.7851)

4. Secondary Outcome Measure:

Measure Title	Average Daily Pain Intensity Scores, Averaged Per Week by Treatment, During the Maintenance Phase.
Measure Description	Participants were asked to record their "average pain over the last 24 hours" pain intensity each evening. Average pain scores are the averages of all scores recorded during each week. 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".
Time Frame	Day 18 through Day 43 (End of Maintenance Phase)
Safety Issue?	No

Analysis Population Description

Full Analysis Set (Maintenance Period). Last observation carried forward.

Reporting Groups

	Description
Tapentadol Prolonged Release (Maintenance Phase)	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.
Matching Placebo After Tapentadol in the Titration Phase	Oral Tapentadol 100 mg to 250 mg twice daily. Participants randomized to placebo in the maintenance phase received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off the tapentadol dose they had received in the Titration Phase. From the 4th day (Day 18) all participants received matching placebo in the maintenance (i.e. randomized withdrawal) phase.

	Description
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.

Measured Values

	Tapentadol Prolonged Release (Maintenance Phase)	Matching Placebo After Tapentadol in the Titration Phase	Morphine Controlled Release
Number of Participants Analyzed	105	111	109
Average Daily Pain Intensity Scores, Averaged Per Week by Treatment, During the Maintenance Phase. [units: units on a scale] Mean (Standard Deviation)			
Prior to start of Maintenance Phase	3.198 (1.2043)	2.928 (1.2353)	2.928 (1.4106)
End of Week 1 of the Maintenance Phase	3.220 (1.2385)	3.115 (1.3799)	2.903 (1.4645)
End of Week 2 of the Maintenance Phase	3.248 (1.3724)	3.005 (1.5723)	2.858 (1.4783)
End of Week 3 of the Maintenance Phase	3.129 (1.3267)	3.055 (1.6702)	2.775 (1.4312)
End of Week 4 of the Maintenance Phase	3.121 (1.3768)	3.095 (1.7349)	2.768 (1.5065)

5. Secondary Outcome Measure:

Measure Title	Current Pain Intensity Scores, Averaged Per Week, During the Titration Phase in the Tapentadol Arm.
Measure Description	Participants were asked to record their current pain intensity in the morning and evening. Average pain scores are the averages of all scores recorded during each week. 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".
Time Frame	Day 1 through Day 14 (End of Titration Phase)
Safety Issue?	No

Analysis Population Description

Full Analysis Set (Titration Phase), observed.

Reporting Groups

	Description
Tapentadol Prolonged Release (Titration Phase)	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.

Measured Values

	Tapentadol Prolonged Release (Titration Phase)
Number of Participants Analyzed	331
Current Pain Intensity Scores, Averaged Per Week, During the Titration Phase in the Tapentadol Arm. [units: units on a scale] Mean (Standard Deviation)	
Start of Titration (N = 320)	6.344 (1.4568)
End of Week 1 (N = 331)	5.326 (1.7650)
End of Week 2 (N = 302)	4.049 (1.8015)

6. Secondary Outcome Measure:

Measure Title	Current Pain Intensity Scores, Averaged Per Week, During the Titration Phase in the Morphine Arm.
Measure Description	Participants were asked to record their current pain intensity in the morning and evening. Average pain scores are the averages of all scores recorded during the during each week. 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".
Time Frame	Day 1 through Day 14 (End of Titration Phase)
Safety Issue?	No

Analysis Population Description

Observed, i.e. participants contributing data via their electronic diary.

Reporting Groups

	Description
Morphine Controlled Release (Titration Phase)	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.

Measured Values

	Morphine Controlled Release (Titration Phase)
Number of Participants Analyzed	157
Current Pain Intensity Scores, Averaged Per Week, During the Titration Phase in the Morphine Arm. [units: units on a scale] Mean (Standard Deviation)	
Start of Titration (N = 150)	6.258 (1.5609)
End of Week 1 (N = 157)	4.937 (1.9080)
End of Week 2 (N = 136)	3.690 (1.8365)

7. Secondary Outcome Measure:

Measure Title	Current Pain Intensity Scores, Averaged Per Week by Treatment, During the Maintenance Phase.
Measure Description	Participants were asked to record their current pain intensity in the morning and evening. Average pain scores are the averages of all scores recorded during the 3 days prior to re-randomization or during each week. 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".
Time Frame	Day 15 through Day 43 (End of Maintenance Phase)
Safety Issue?	No

Analysis Population Description

Full Analysis Set (Maintenance Period). Last observation carried forward.

Reporting Groups

	Description
Tapentadol Prolonged Release (Maintenance Phase)	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.
Matching Placebo After Tapentadol in the Titration Phase	Oral Tapentadol 100 mg to 250 mg twice daily. Participants randomized to placebo in the maintenance phase received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off the tapentadol dose they had received in the Titration Phase. From the 4th day (Day 18) all participants received matching placebo in the maintenance (i.e. randomized withdrawal) phase.
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.

Measured Values

	Tapentadol Prolonged Release (Maintenance Phase)	Matching Placebo After Tapentadol in the Titration Phase	Morphine Controlled Release
Number of Participants Analyzed	105	111	109
Current Pain Intensity Scores, Averaged Per Week by Treatment, During the Maintenance Phase. [units: units on a scale] Mean (Standard Deviation)			
Prior to start of maintenance phase	3.1444 (1.16485)	2.8686 (1.19387)	2.832 (1.3895)
End of Week 1	3.0869 (1.22550)	3.0073 (1.32110)	2.780 (1.3706)
End of Week 2	3.1148 (1.27905)	2.8683 (1.47838)	2.790 (1.4170)
End of Week 3	3.0137 (1.26515)	2.9122 (1.60299)	2.733 (1.4512)
End of Week 4	3.0002 (1.37551)	2.9220 (1.68601)	2.728 (1.4481)

8. Secondary Outcome Measure:

Measure Title	Use of Rescue Medication in the Titration Phase.
Measure Description	The number of participants using rescue medication morphine sulfate immediate release 10 mg tablets in the titration phase were counted. This data was captured in an electronic diary. During the trial, morphine immediate release 10 mg was allowed as required without a maximum dose defined. However, participants were only re-randomized if their mean consumption of rescue medication was less or equal to 2 doses (20 mg) per day during the last 3 days of the titration phase).
Time Frame	Day 1 through Day 14 (End of Titration Phase)
Safety Issue?	No

Analysis Population Description

Full Analysis Set (Titration phase), observed.

Reporting Groups

	Description
Tapentadol Prolonged Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.

	Description
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.

Measured Values

	Tapentadol Prolonged Release	Morphine Controlled Release
Number of Participants Analyzed	335	157
Use of Rescue Medication in the Titration Phase. [units: participants]	241	91

9. Secondary Outcome Measure:

Measure Title	Number of Participants Using Immediate Release Morphine Rescue Medication in the Maintenance Phase
Measure Description	Participants were issued morphine 10 mg immediate release medication. The number of participants using rescue medication morphine sulfate immediate release 10 mg tablets in the maintenance phase were counted. This use of morphine immediate release was captured in each participant's electronic diary.
Time Frame	Day 15 through Day 43 (End of Maintenance Phase)
Safety Issue?	No

Analysis Population Description

Full Analysis Set (Maintenance phase), observed.

Reporting Groups

	Description
Tapentadol Prolonged Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.
Matching Placebo After Tapentadol in Titration Phase	Oral Tapentadol 100 mg to 250 mg twice daily. Participants randomized to placebo in the maintenance phase received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off the tapentadol dose they had received in the Titration Phase. From the 4th day (Day 18) all participants received matching placebo in the maintenance (i.e. randomized withdrawal) phase.

Measured Values

	Tapentadol Prolonged Release	Morphine Controlled Release	Matching Placebo After Tapentadol in Titration Phase
Number of Participants Analyzed	105	109	111
Number of Participants Using Immediate Release Morphine Rescue Medication in the Maintenance Phase [units: participants]	75	67	80

10. Secondary Outcome Measure:

Measure Title	The Average Mean Total Daily Dose of Rescue Medication.
Measure Description	Mean total daily dose of rescue medication morphine sulphate immediate release tablets in milligrams per day (mg/day).
Time Frame	Day 1 (Start of Titration Phase) through Day 43 (End of Maintenance Phase)
Safety Issue?	No

Analysis Population Description

Full analysis set for each phase of the trial, observed.

Reporting Groups

	Description
Tapentadol Prolonged Release (Titration Phase)	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.
Morphine Controlled Release Titration Phase	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses
Tapentadol Prolonged Release (Maintenance Phase)	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.
Matching Placebo After Tapentadol in Titration Phase	Oral Tapentadol 100 mg to 250 mg twice daily in the titration phase. Followed by matching placebo in the maintenance (i.e. randomized withdrawal phase).
Morphine Controlled Release Maintenance Phase	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.

Measured Values

	Tapentadol Prolonged Release (Titration Phase)	Morphine Controlled Release Titration Phase	Tapentadol Prolonged Release (Maintenance Phase)	Matching Placebo After Tapentadol in Titration Phase	Morphine Controlled Release Maintenance Phase
Number of Participants Analyzed	335	157	105	111	109
The Average Mean Total Daily Dose of Rescue Medication. [units: milligrams per day of morphine rescue] Mean (Standard Deviation)	13.31 (17.41)	8.87 (12.50)	11.2 (12.739)	13.65 (13.666)	8.91 (14.951)

11. Secondary Outcome Measure:

Measure Title	Changes in the Short Form 36® Health Survey (SF-36®) During the Titration Phase.
Measure Description	The Short Form 36 (SF-36) includes several brief questions on 8 aspects, (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health) that a participant was asked to score over the last week. Low scores on the Physical Component Summary measure indicate limitations in physical functioning, e.g. a high degree of bodily pain and physical limitations etc. For the Mental Component Summary measure, a low score is indicative of frequent psychological distress, social and role disability due to emotional problems etc. The theoretical range for the physical component score is 12.3279 to 59.6503. The theoretical range for the mental component score is 13.5313 to 59.6503. Positive values for changes in the component scores indicate an improvement.
Time Frame	Day 1 (Start of Titration); Day 14 (End of Titration Phase)
Safety Issue?	No

Analysis Population Description

Full analysis set (Titration Period), observed. Start of Titration and Endpoint Titration observations.

Reporting Groups

	Description
Tapentadol Prolonged Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.

Measured Values

	Tapentadol Prolonged Release	Morphine Controlled Release
Number of Participants Analyzed	285	131
Changes in the Short Form 36® Health Survey (SF-36®) During the Titration Phase. [units: units on a scale] Mean (Standard Deviation)		
Mental Component Summary	1.3 (10.63)	1.1 (11.78)
Physical Component Summary	2.0 (5.99)	3.1 (6.48)

12. Secondary Outcome Measure:

Measure Title	Changes in the Short Form 36® Health Survey (SF-36®) During the Maintenance Phase.
Measure Description	The Short Form 36 (SF-36) includes several brief questions on 8 aspects, (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health) that a participant was asked to score over the last week. Low scores on the Physical Component Summary measure indicate limitations in physical functioning, e.g. a high degree of bodily pain and physical limitations etc. For the Mental Component Summary measure, a low score is indicative of frequent psychological distress, social and role disability due to emotional problems etc. The theoretical range for the physical component score is 12.3279 to 59.6503. The theoretical range for the mental component score is 13.5313 to 59.6503. Positive values for changes in the component scores indicate an improvement.
Time Frame	Day 15 (Start of Maintenance); Day 43 (End of Maintenance Phase)
Safety Issue?	No

Analysis Population Description

Full analysis set (Maintenance Phase), observed. Start of Maintenance and Endpoint Maintenance observations.

Reporting Groups

	Description
Tapentadol Extended Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.

	Description
Matching Placebo After Tapentadol in Titration Phase	Oral Tapentadol 100 mg to 250 mg twice daily. Participants randomized to placebo in the maintenance phase received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off the tapentadol dose they had received in the Titration Phase. From the 4th day (Day 18) all participants received matching placebo in the maintenance (i.e. randomized withdrawal) phase.

Measured Values

	Tapentadol Extended Release	Morphine Controlled Release	Matching Placebo After Tapentadol in Titration Phase
Number of Participants Analyzed	95	97	103
Changes in the Short Form 36® Health Survey (SF-36®) During the Maintenance Phase. [units: units on a scale] Mean (Standard Deviation)			
Mental Component Summary	-0.4 (10.81)	-2.164 (9.42)	-1.5 (9.99)
Physical Component Summary	-1.1 (6.26)	-0.671 (7.21)	-0.9 (6.29)

13. Secondary Outcome Measure:

Measure Title	Change in the EuroQoL (EQ-5D) Health Status Index (United Kingdom Time Trade-off Value Set) Change From Start of Titration to Endpoint Titration.
Measure Description	The participant scores the EuroQol-5D. The EuroQoL-5D is a five dimensional health state classification. Each dimension is assessed on a 3-point ordinal scale (1 = no problems, 2 = some problems, 3 = extreme problems). The responses to the five EQ-5D dimensions are scored using a utility-weighted algorithm to derive an EQ-5D health status index score between 0 to 1, with 1.00 indicating "full health" and 0 representing dead. A positive change in the mean indicates that during this phase the health status improved. A positive change indicates an improvement in health. The minimal important difference is 0.074 (range -0.011 to 0.140).
Time Frame	Day 1 (Start of Titration); Day 14 (End of Titration Phase)
Safety Issue?	No

Analysis Population Description

Full analysis set (Titration Phase), observed.

Reporting Groups

	Description
Tapentadol Prolonged Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.

Measured Values

	Tapentadol Prolonged Release	Morphine Controlled Release
Number of Participants Analyzed	286	132
Change in the EuroQoL (EQ-5D) Health Status Index (United Kingdom Time Trade-off Value Set) Change From Start of Titration to Endpoint Titration. [units: units on a scale] Mean (Standard Deviation)	0.093 (0.3294)	0.131 (0.3162)

14. Secondary Outcome Measure:

Measure Title	Health Related Quality of Life: EuroQol-5D Health State Visual Analog Scale (VAS) Titration Phase.
Measure Description	EuroQoL-5D Health State Visual Analog Scale (VAS) is a participant rated questionnaire to assess health-related quality of life in terms of a single index value. The VAS component rates current health state on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state); higher scores indicate better health. The values indicated represent the change from Day 1, a positive value indicates an improvement since the start of treatment.
Time Frame	Day 1 (Start of Titration); Day 14 (End of Titration Phase)
Safety Issue?	No

Analysis Population Description

Full analysis set (Titration Phase), observed.

Reporting Groups

	Description
Tapentadol Prolonged Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.

Measured Values

	Tapentadol Prolonged Release	Morphine Controlled Release
Number of Participants Analyzed	286	131
Health Related Quality of Life: EuroQol-5D Health State Visual Analog Scale (VAS) Titration Phase. [units: units on a scale] Mean (Standard Deviation)	3.8 (22.63)	5.6 (20.42)

15. Secondary Outcome Measure:

Measure Title	Change in the EuroQoL (EQ-5D) Health Status Index (United Kingdom Time Trade-off Value Set) Over Time in the Maintenance Phase for Tapentadol and the Placebo Randomized Withdrawal Treatment Arms.
Measure Description	The participant scores the EuroQol-5D. The EuroQoL-5D is a five dimensional health state classification. Each dimension is assessed on a 3-point ordinal scale (1 = no problems, 2 = some problems, 3 = extreme problems). The responses to the five EQ-5D dimensions are scored using a utility-weighted algorithm to derive an EQ-5D health status index score between 0 to 1, with 1.00 indicating "full health" and 0 representing dead. A negative change in the mean indicates a worsening in health status since the beginning of the maintenance phase. A positive change indicates an improvement in health. The minimal important difference in the Health Status Index is 0.074 (range -0.011 to 0.140).
Time Frame	Day 15 (Start of Maintenance); Day 43 (End of Maintenance Phase)
Safety Issue?	No

Analysis Population Description

Full Analysis Set (Maintenance Phase), observed. Start of Maintenance and Endpoint Maintenance observations. No morphine treatment analysis was planned.

Reporting Groups

	Description
Tapentadol Prolonged Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.
Matching Placebo After Tapentadol in Titration Phase	Oral Tapentadol 100 mg to 250 mg twice daily. Participants randomized to placebo in the maintenance phase received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off the tapentadol dose they had received in the Titration Phase. From the 4th day (Day 18) all participants received matching placebo in the maintenance (i.e. randomized withdrawal) phase.

Measured Values

	Tapentadol Prolonged Release	Matching Placebo After Tapentadol in Titration Phase
Number of Participants Analyzed	95	103
Change in the EuroQoL (EQ-5D) Health Status Index (United Kingdom Time Trade-off Value Set) Over Time in the Maintenance Phase for Tapentadol and the Placebo Randomized Withdrawal Treatment Arms. [units: units on a scale] Mean (Standard Deviation)	-0.0626 (0.3130)	-0.058 (0.2909)

16. Secondary Outcome Measure:

Measure Title	Changes in Health Related Quality of Life: EuroQol-5D Health State Visual Analog Scale (VAS) Maintenance Phase.
Measure Description	EuroQoL-5D Health State Visual Analog Scale (VAS) is a participant rated questionnaire to assess health-related quality of life in terms of a single index value. The VAS component rates current health state on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state); higher scores indicate a better health state. The values indicated represent the change from Day 15, a negative mean value indicates a worsening of health-related quality of life since the start of the maintenance phase.
Time Frame	Day 15 (Start of Maintenance); Day 43 (End of Maintenance Phase)
Safety Issue?	No

Analysis Population Description

Full Analysis Set (Maintenance Phase), observed. Start of Maintenance and Endpoint Maintenance observations.

Reporting Groups

	Description
Tapentadol Prolonged Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.

	Description
Matching Placebo After Tapentadol in the Titration Phase	Oral Tapentadol 100 mg to 250 mg twice daily. Participants randomized to placebo in the maintenance phase received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off the tapentadol dose they had received in the Titration Phase. From the 4th day (Day 18) all participants received matching placebo in the maintenance (i.e. randomized withdrawal) phase.

Measured Values

	Tapentadol Prolonged Release	Morphine Controlled Release	Matching Placebo After Tapentadol in the Titration Phase
Number of Participants Analyzed	95	97	103
Changes in Health Related Quality of Life: EuroQol-5D Health State Visual Analog Scale (VAS) Maintenance Phase. [units: units on a scale] Mean (Standard Deviation)	-2.1 (19.80)	-0.6 (16.94)	-1.5 (18.55)

17. Secondary Outcome Measure:

Measure Title	Patient Global Impression of Change
Measure Description	In the Patient Global Impression of Change (PGIC) the participant is asked "Since I began study treatment, my overall status is". The participant is asked to circle one of seven categories. Scores range from very much improved to very much worse. The question was asked at the end of the maintenance phase with reference to the start of the maintenance phase where the participant continued at the dose that was effective at the end of the Titration Phase.
Time Frame	Day 43 (End of Maintenance Phase)
Safety Issue?	No

Analysis Population Description

Full Analysis Set, observed.

Reporting Groups

	Description
Tapentadol Prolonged Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.

	Description
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.
Matching Placebo After Tapentadol in Titration Phase	Oral Tapentadol 100 mg to 250 mg twice daily. Participants randomized to placebo in the maintenance phase received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off the tapentadol dose they had received in the Titration Phase. From the 4th day (Day 18) all participants received matching placebo in the maintenance (i.e. randomized withdrawal) phase.

Measured Values

	Tapentadol Prolonged Release	Morphine Controlled Release	Matching Placebo After Tapentadol in Titration Phase
Number of Participants Analyzed	94	97	103
Patient Global Impression of Change [units: participants]			
Very Much Improved	4	6	6
Much Improved	29	23	31
Minimally Improved	33	38	38
No Change	10	12	11
Minimally Worse	10	6	9
Much Worse	7	12	7
Very Much Worse	1	0	1

18. Secondary Outcome Measure:

Measure Title	Quality of Sleep (Sleep Questionnaire) in the Titration Phase.
Measure Description	Participants were asked the following question: "Please rate the overall quality of your sleep last night?" The quality of sleep from the start of the titration phase to the end of the titration phase was measured. The participant could choose one of the following options: Excellent, good, fair and poor.
Time Frame	Day 1 (Start of Titration); Day 14 (end of Titration Phase)
Safety Issue?	No

Analysis Population Description

Full Analysis Set (Titration Phase), observed. Tapentadol: 302 participants dosed gave a response at the start of titration and from 309 participants at the end of titration.

Morphine: 143 participants dosed gave a response at the start of titration and from 142 participants at the end of titration.

Reporting Groups

	Description
Tapentadol Prolonged Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.

Measured Values

	Tapentadol Prolonged Release	Morphine Controlled Release
Number of Participants Analyzed	338	158
Quality of Sleep (Sleep Questionnaire) in the Titration Phase. [units: participants]		
Excellent at the start of the titration phase	9	4
Excellent at the end of the titration phase	12	3
Good at the start of the titration phase	77	47
Good at the end of the titration phase	139	64
Fair at the start of the titration phase	142	51
Fair at the end of the titration phase	121	61
Poor at the start of the titration phase	74	41
Poor at the end of the titration phase	37	14
Not completed at the start of titration	36	15
Not completed at the end of the titration	29	16

19. Secondary Outcome Measure:

Measure Title	Quality of Sleep (Sleep Questionnaire) During the Maintenance Phase of the Trial.

Measure Description	Participants were asked the following question: "Please rate the overall quality of your sleep last night?" The quality of sleep from the start of maintenance to the completion of treatment is reported. The participant could choose one of the following options: Excellent, good, fair and poor.
Time Frame	Day 15 (Start of Maintenance); Day 43 (End of Maintenance Phase)
Safety Issue?	No

Analysis Population Description

FAS (Maintenance Phase) Last Observation Carried Forward for participants re-randomized.

Tapentadol: 105 participants responded at the start and 103 participants at the end.

Morphine: 108 participants responded at the start and 107 participants at the end.

Placebo: 110 participants responded at the start and 107 participants at the end.

Reporting Groups

	Description
Tapentadol Prolonged Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase
Matching Placebo After Tapentadol in Titration Phase	Oral Tapentadol 100 mg to 250 mg twice daily. Participants randomized to placebo in the maintenance phase received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off the tapentadol dose they had received in the Titration Phase. From the 4th day (Day 18) all participants received matching placebo in the maintenance (i.e. randomized withdrawal) phase.

Measured Values

	Tapentadol Prolonged Release	Morphine Controlled Release	Matching Placebo After Tapentadol in Titration Phase
Number of Participants Analyzed	105	108	110
Quality of Sleep (Sleep Questionnaire) During the Maintenance Phase of the Trial. [units: participants]			
Excellent at start of maintenance phase	8	2	4
Excellent at the end of maintenance phase	8	9	8
Good at start of maintenance phase	55	51	60

	Tapentadol Prolonged Release	Morphine Controlled Release	Matching Placebo After Tapentadol in Titration Phase
Good at the end of maintenance phase	43	40	49
Fair at start of maintenance phase	35	50	42
Fair at the end of maintenance phase	38	53	37
Poor at start of maintenance phase	7	5	4
Poor at the end of maintenance phase	14	5	13

20. Secondary Outcome Measure:

Measure Title	Clinical Opioid Withdrawal Scale (COWS) at the End of the Titration Phase.
Measure Description	This instrument was developed by the National Institute on Drug Abuse. The physical components of withdrawal are primarily evaluated and based on questions and clinical observations. The possible opioid withdrawal effects are assessed using the Clinical Opioid Withdrawal Score (COWS). The COWS is a clinician rated 11-item scale that primarily evaluates the physical components of opioid withdrawal and is based on questions and clinical observations. Responses are rated on a Likert-type scale ranging from 0 to 4 or 5 depending on the item. The total COWS score is the sum of all individual items. The following withdrawal categories are based on the total COWS score: • None: total score below 5; • Mild: total score from 5 to 12; • Moderate: total score 13 to 24; • Moderately Severe: total score 25 to 36; • Severe: total score above 36. The investigator completes the COWS after participants discontinued trial medication 2 to less than 5 days after last intake of trial medication.
Time Frame	Day 14 (End of Titration Phase)
Safety Issue?	Yes

Analysis Population Description

Safety Analysis Set (Titration Phase). Participants that took at least one dose of trial medication in the titration phase, and discontinued trial medication at the end or during the titration phase and did not continue on other opioid medication.

Reporting Groups

	Description
Tapentadol Prolonged Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.

	Description
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.
Matching Placebo After Tapentadol in Titration Phase	Oral Tapentadol 100 mg to 250 mg twice daily. Followed by matching placebo in the maintenance (i.e. randomized withdrawal phase).

Measured Values

	Tapentadol Prolonged Release	Morphine Controlled Release	Matching Placebo After Tapentadol in Titration Phase
Number of Participants Analyzed	7	6	9
Clinical Opioid Withdrawal Scale (COWS) at the End of the Titration Phase. [units: participants]			
None	7	5	8
Mild	0	1	1
Moderate	0	0	0
Moderately Severe	0	0	0
Severe	0	0	0

21. Secondary Outcome Measure:

Measure Title	Clinical Opioid Withdrawal Score (COWS) at the End of the Maintenance Phase.
Measure Description	This instrument was developed by the National Institute on Drug Abuse. The physical components of withdrawal are primarily evaluated and based on questions and clinical observations. The possible opioid withdrawal effects are assessed using the Clinical Opioid Withdrawal Score (COWS). The COWS is a clinician rated 11-item scale that primarily evaluates the physical components of opioid withdrawal and is based on questions and clinical observations. Responses are rated on a Likert-type scale ranging from 0 to 4 or 5 depending on the item. The total COWS score is the sum of all individual items. The following withdrawal categories are based on the total COWS score: • None: total score below 5; • Mild: total score from 5 to 12; • Moderate: total score 13 to 24; • Moderately Severe: total score 25 to 36; • Severe: total score above 36. The investigator completes the COWS after participants discontinued trial medication 2 to less than 5 days after last intake of trial medication.

Time Frame	Day 43 (End of Maintenance Phase)
Safety Issue?	Yes

Analysis Population Description

Safety Analysis Set. Participants that did not discontinue due to adverse event during the first week of the maintenance phase and started opioid after last study medication.

Reporting Groups

	Description
Tapentadol Prolonged Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.
Matching Placebo After Tapentadol in Titration Phase	Oral Tapentadol 100 mg to 250 mg twice daily. Participants randomized to placebo in the maintenance phase received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off the tapentadol dose they had received in the Titration Phase. From the 4th day (Day 18) all participants received matching placebo in the maintenance (i.e. randomized withdrawal) phase.

Measured Values

	Tapentadol Prolonged Release	Morphine Controlled Release	Matching Placebo After Tapentadol in Titration Phase
Number of Participants Analyzed	26	29	29
Clinical Opioid Withdrawal Score (COWS) at the End of the Maintenance Phase. [units: participants]			
None	19	23	21
Mild	7	6	8
Moderate	0	0	0
Moderately Severe	0	0	0
Severe	0	0	0

22. Secondary Outcome Measure:

Measure Title	Change in the Patient Assessment of Constipation Symptoms (PAC-SYM) During the Titration Phase
Measure Description	The Constipation Assessment (PAC-SYM) is a 12-item self-report questionnaire that assesses the severity of symptoms of constipation. Participants are asked "How severe have each of these symptoms been in the last two weeks?" e.g. "Pain in your stomach". There are 3 subscales: 4 questions on Abdominal symptoms, 3 questions on rectal symptoms and 5 questions on stool symptoms. Responses are rated on a 5-point Likert Scale ranging from 0 (absence of symptom) to 4 (very severe symptoms). The changes in overall mean and in each of the mean sub-scores vary theoretically from -4 to +4 (where a change of +4 would indicate a change from not present to very severe symptom). If the changes in the overall or subscale mean scores are positive then there is a worsening in symptoms associated with constipation from the start to the end of the titration phase.
Time Frame	Day 1 (Start of Titration); Day 14 (End of Titration Phase)
Safety Issue?	Yes

Analysis Population Description

Per Protocol Set (Titration Phase), observed. Start of Titration and Endpoint Titration observations.

Reporting Groups

	Description
Tapentadol Prolonged Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.

Measured Values

	Tapentadol Prolonged Release	Morphine Controlled Release
Number of Participants Analyzed	216	93
Change in the Patient Assessment of Constipation Symptoms (PAC-SYM) During the Titration Phase [units: units on a scale] Mean (Standard Deviation)		
Overall abdominal subscale	-0.062 (0.6507)	-0.076 (0.7242)
Overall rectal subscale	0.059 (0.6442)	-0.006 (0.6736)
Overall stool subscale	0.02 (0.812)	0.13 (0.870)
Overall PAC-SYM score	0.003 (0.5782)	0.027 (0.6154)

23. Secondary Outcome Measure:

Measure Title	Change in the Patient Assessment of Constipation Symptoms (PAC-SYM) During the Maintenance Phase
Measure Description	The Constipation Assessment (PAC-SYM) is a 12-item self-report questionnaire that assesses the severity of symptoms of constipation. Participants are asked "How severe have each of these symptoms been in the last two weeks?" e.g. "Pain in your stomach". There are 3 subscales: 4 questions on Abdominal symptoms, 3 questions on rectal symptoms and 5 questions on stool symptoms. Responses are rated on a 5-point Likert Scale ranging from 0 (absence of symptom) to 4 (very severe symptoms). The changes in overall mean and in each of the mean sub-scores vary theoretically from -4 to +4 (where a change of +4 would indicate a change from not present to very severe symptom). If the changes in the overall or subscale mean scores are positive then there is a worsening in symptoms associated with constipation from the start to the end of the maintenance phase. A negative mean change indicates an improvement.
Time Frame	Day 15 (Start of Maintenance); Day 43 (End of Maintenance Phase)
Safety Issue?	Yes

Analysis Population Description

Safety Analysis Set (Maintenance Phase), observed. Start of Maintenance and Endpoint Maintenance observations.

Reporting Groups

	Description
Tapentadol Prolonged Release	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.
Morphine Controlled Release	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses. The participant continued at the dose that was effective at the end of the Titration Phase.
Matching Placebo After Tapentadol in Titration Phase	Oral Tapentadol 100 mg to 250 mg twice daily. Participants randomized to placebo in the maintenance phase received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off the tapentadol dose they had received in the Titration Phase. From the 4th day (Day 18) all participants received matching placebo in the maintenance (i.e. randomized withdrawal) phase.

Measured Values

	Tapentadol Prolonged Release	Morphine Controlled Release	Matching Placebo After Tapentadol in Titration Phase
Number of Participants Analyzed	95	96	103
Change in the Patient Assessment of Constipation Symptoms (PAC-SYM) During the Maintenance Phase [units: units on a scale] Mean (Standard Deviation)			

	Tapentadol Prolonged Release	Morphine Controlled Release	Matching Placebo After Tapentadol in Titration Phase
Overall abdominal subscale	-0.105 (0.6280)	0.026 (0.5966)	-0.075 (0.5330)
Overall rectal subscale	0.017 (0.5086)	0.014 (0.5090)	-0.033 (0.5822)
Overall stool subscale	-0.07 (0.743)	0.03 (0.724)	-0.03 (0.667)
Overall PAC-SYM score	-0.059 (0.4992)	0.024 (0.4584)	-0.048 (0.4771)

Reported Adverse Events

Time Frame	Serious adverse events reported any time after treatment is taken, to within 30 days after end of treatment.
Additional Description	[Not specified]

Reporting Groups

	Description
Tapentadol Prolonged Release (Titration Phase)	Oral Tapentadol 100 mg to 250 mg twice daily. Tablet taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.
Morphine Controlled Release (Titration Phase)	Oral Morphine 40 mg to 100 mg twice daily. Capsule taken orally, twice daily, morning & evening with preferably 12 hours (not less than 6 hours) between doses.
Tapentadol Prolonged Release (Maintenance Phase)	Oral Tapentadol 100 mg to 250 mg twice daily. The participant continued at the dose that was effective at the end of the Titration Phase.
Matching Placebo After Tapentadol in Titration Phase	Oral Tapentadol 100 mg to 250 mg twice daily. Participants randomized to placebo in the maintenance phase received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off the tapentadol dose they had received in the Titration Phase. From the 4th day (Day 18) all participants received matching placebo in the maintenance (i.e. randomized withdrawal) phase.
Morphine Controlled Release (Maintenance Phase)	Oral Morphine 40 mg to 100 mg twice daily. The dose that was effective at the end of the Titration Phase.

Serious Adverse Events

	Tapentadol Prolonged Release (Titration Phase)	Morphine Controlled Release (Titration Phase)	Tapentadol Prolonged Release (Maintenance Phase)	Matching Placebo After Tapentadol in Titration Phase	Morphine Controlled Release (Maintenance Phase)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	25/338 (7.4%)	6/158 (3.8%)	12/106 (11.32%)	10/112 (8.93%)	6/109 (5.5%)
Blood and lymphatic system disorders					
Anaemia [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	1/109 (0.92%)
Anaemia [A] †	0/338 (0%)	0/158 (0%)	0/106 (0%)	1/112 (0.89%)	1/109 (0.92%)
Febrile neutropenia [A] †	0/338 (0%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	1/109 (0.92%)
Thrombocytopenia [A] †	0/338 (0%)	0/158 (0%)	0/106 (0%)	1/112 (0.89%)	0/109 (0%)
Cardiac disorders					
Cardio-respiratory arrest [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Cardiovascular insufficiency [A] *	0/338 (0%)	0/158 (0%)	2/106 (1.89%)	0/112 (0%)	0/109 (0%)
Cor pulmonale acute [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Coronary artery disease [A] *	0/338 (0%)	0/158 (0%)	0/106 (0%)	1/112 (0.89%)	0/109 (0%)
Endocrine disorders					
Adrenocortical insufficiency acute [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Gastrointestinal disorders					
Ascites [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	2/112 (1.79%)	0/109 (0%)
Diarrhoea [A] *	2/338 (0.59%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Haematemesis [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Intestinal perforation [A] *	0/338 (0%)	0/158 (0%)	1/106 (0.94%)	0/112 (0%)	0/109 (0%)
Melaena [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Vomiting [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
General disorders					

	Tapentadol Prolonged Release (Titration Phase)	Morphine Controlled Release (Titration Phase)	Tapentadol Prolonged Release (Maintenance Phase)	Matching Placebo After Tapentadol in Titration Phase	Morphine Controlled Release (Maintenance Phase)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Asthenia [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Death [A] *	0/338 (0%)	0/158 (0%)	2/106 (1.89%)	0/112 (0%)	0/109 (0%)
General physical health deterioration [A] *	0/338 (0%)	0/158 (0%)	1/106 (0.94%)	0/112 (0%)	0/109 (0%)
Hospitalization due to travel problems [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Pyrexia [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Hepatobiliary disorders					
Hepatic failure [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Infections and infestations					
Lobar pneumonia [A] *	0/338 (0%)	0/158 (0%)	0/106 (0%)	1/112 (0.89%)	0/109 (0%)
Peritonitis [A] *	0/338 (0%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	1/109 (0.92%)
Pneumonia [A] *	0/338 (0%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	1/109 (0.92%)
Injury, poisoning and procedural complications					
Femur fracture [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Lower limb fracture [A] *	0/338 (0%)	0/158 (0%)	0/106 (0%)	1/112 (0.89%)	0/109 (0%)
Spinal compression fracture [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Investigations					
Blood urea increased [A] †	0/338 (0%)	0/158 (0%)	1/106 (0.94%)	0/112 (0%)	0/109 (0%)
Musculoskeletal and connective tissue disorders					
Arthralgia [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Muscular weakness [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Osteonecrosis [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)

	Tapentadol Prolonged Release (Titration Phase)	Morphine Controlled Release (Titration Phase)	Tapentadol Prolonged Release (Maintenance Phase)	Matching Placebo After Tapentadol in Titration Phase	Morphine Controlled Release (Maintenance Phase)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Trismus [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Metastases to central nervous system [A] *	1/338 (0.3%)	1/158 (0.63%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Neoplasm malignant [A] *	5/338 (1.48%)	1/158 (0.63%)	4/106 (3.77%)	2/112 (1.79%)	1/109 (0.92%)
Tumour pain [A] *	1/338 (0.3%)	0/158 (0%)	1/106 (0.94%)	0/112 (0%)	0/109 (0%)
Psychiatric disorders					
Confusional state [A] *	0/338 (0%)	1/158 (0.63%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Withdrawal syndrome [A] †	0/338 (0%)	0/158 (0%)	0/106 (0%)	1/112 (0.89%)	0/109 (0%)
Renal and urinary disorders					
Renal failure acute [A] *	0/338 (0%)	0/158 (0%)	1/106 (0.94%)	0/112 (0%)	0/109 (0%)
Reproductive system and breast disorders					
Female genital tract fistula [A] *	0/338 (0%)	1/158 (0.63%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Respiratory, thoracic and mediastinal disorders					
Acute respiratory failure [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Chronic obstructive pulmonary disease [A] *	0/338 (0%)	0/158 (0%)	0/106 (0%)	1/112 (0.89%)	0/109 (0%)
Dyspnoea [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	1/109 (0.92%)
Pulmonary embolism [A] *	1/338 (0.3%)	1/158 (0.63%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Pulmonary haemorrhage [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Pulmonary oedema [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Respiratory failure [A] *	0/338 (0%)	0/158 (0%)	1/106 (0.94%)	0/112 (0%)	0/109 (0%)
Vascular disorders					

	Tapentadol Prolonged Release (Titration Phase)	Morphine Controlled Release (Titration Phase)	Tapentadol Prolonged Release (Maintenance Phase)	Matching Placebo After Tapentadol in Titration Phase	Morphine Controlled Release (Maintenance Phase)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Deep vein thrombosis [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Superior vena cava syndrome [A] *	1/338 (0.3%)	0/158 (0%)	0/106 (0%)	0/112 (0%)	0/109 (0%)
Thrombosis [A] *	0/338 (0%)	1/158 (0.63%)	0/106 (0%)	0/112 (0%)	1/109 (0.92%)

† Indicates events were collected by systematic assessment.
* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 15.0

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Tapentadol Prolonged Release (Titration Phase)	Morphine Controlled Release (Titration Phase)	Tapentadol Prolonged Release (Maintenance Phase)	Matching Placebo After Tapentadol in Titration Phase	Morphine Controlled Release (Maintenance Phase)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	112/338 (33.14%)	80/158 (50.63%)	41/106 (38.68%)	34/112 (30.36%)	37/109 (33.94%)
Gastrointestinal disorders					
Constipation [A] *	48/338 (14.2%)	28/158 (17.72%)	12/106 (11.32%)	13/112 (11.61%)	12/109 (11.01%)
Dry Mouth [A] *	4/338 (1.18%)	10/158 (6.33%)	3/106 (2.83%)	2/112 (1.79%)	1/109 (0.92%)
Nausea [A] *	42/338 (12.43%)	38/158 (24.05%)	16/106 (15.09%)	17/112 (15.18%)	11/109 (10.09%)
Vomiting [A] *	17/338 (5.03%)	25/158 (15.82%)	8/106 (7.55%)	3/112 (2.68%)	6/109 (5.5%)
General disorders					
Fatigue [A] *	10/338 (2.96%)	8/158 (5.06%)	4/106 (3.77%)	6/112 (5.36%)	6/109 (5.5%)
Metabolism and nutrition disorders					
Decreased Appetite [A] *	9/338 (2.66%)	6/158 (3.8%)	8/106 (7.55%)	6/112 (5.36%)	6/109 (5.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					

	Tapentadol Prolonged Release (Titration Phase)	Morphine Controlled Release (Titration Phase)	Tapentadol Prolonged Release (Maintenance Phase)	Matching Placebo After Tapentadol in Titration Phase	Morphine Controlled Release (Maintenance Phase)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Neoplasm Malignant [A] *	3/338 (0.89%)	0/158 (0%)	6/106 (5.66%)	2/112 (1.79%)	3/109 (2.75%)
Nervous system disorders					
Dizziness [A] *	17/338 (5.03%)	10/158 (6.33%)	5/106 (4.72%)	4/112 (3.57%)	0/109 (0%)
Somnolence [A] *	14/338 (4.14%)	10/158 (6.33%)	3/106 (2.83%)	2/112 (1.79%)	6/109 (5.5%)
Skin and subcutaneous tissue disorders					
Hyperhidrosis [A] *	9/338 (2.66%)	7/158 (4.43%)	4/106 (3.77%)	1/112 (0.89%)	7/109 (6.42%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The Sponsor reserves the right to review any publication pertaining to the trial at least 30 days before it is submitted for publication. Neither party has the right to prohibit publication unless publication can be shown to affect possible patent rights.

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