ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 06/14/2016

ClinicalTrials.gov ID: NCT00505414

Study Identification

Unique Protocol ID:	672519
Brief Title:	A Study to Evaluate the Effectiveness and Safety of CG5503 (Tapentadol) in the Treatment of Chronic Tumor Related Pain Compared With Placebo and Morphine
Official Title:	A Randomized Withdrawal, Active- and Placebo-controlled, Double-blind, Multi-center Phase III Trial Assessing Safety and Efficacy of Oral CG5503 (Tapentadol) Prolonged Release (PR*) in Subjects With Moderate to Severe Chronic Malignant Tumor-related Pain. *Prolonged Release and is the Recommended Nomenclature for Use in the European Union (EU). ER Means Extended Release and is the Recommended Nomenclature for Use in the United States of America (USA). "PR" is Synonymous With "ER" and is Interchangeable.
Secondary IDs:	2007-001985-34 [EudraCT Number] KF5503/16 [Grünenthal GmbH]

Study Status

Record Verification:	June 2016
Overall Status:	Terminated [Recall of rescue medication, alternative rescue medication availability issues.]
Study Start:	June 2007
Primary Completion:	February 2009 [Actual]
Study Completion:	May 2009 [Actual]

Sponsor/Collaborators

Sponsor:	Grünenthal GmbH
Responsible Party:	Sponsor
Collaborators:	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Oversight

FDA Regulated?:	Yes
Applicable Trial?:	Section 801 Clinical Trial? Yes Delayed Posting? No
IND/IDE Protocol?:	Yes
IND/IDE Information:	Grantor: CDER IND/IDE Number: 61,345 Serial Number: 211 Has Expanded Access? No
Review Board:	Approval Status: Approved Approval Number: 2489 Board Name: Sterling Institutional Review Board Board Affiliation: Sterling Independent Services, INC Phone: 777 690 Email: sterlingirb@sterlingirb.com
Data Monitoring?:	No
Plan to Share Data?:	
Oversight Authorities:	United States: Food and Drug Administration

Study Description

Brief Summary:	The purpose of this study is to determine whether CG5503 (tapentadol) is effective and safe in the treatment of chronic tumor related pain compared to placebo.
Detailed Description:	Normally chronic tumor related pain is controlled when subjects 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, a newly synthesized drug with an Prolonged Release (ER) formulation, also acts as a centrally acting pain reliever but has a dual mode of action. The aim of this trial is to investigate the effectiveness (level of pain control) and safety (side effects) of Tapentadol Prolonged Release (ER) compared to a tablet with no active ingredient drug (placebo) and a 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, multicenter trial. To maintain the blind all subjects were re-randomized at the start of the maintenance period. To maintain the blind all tapentadol subjects were re-randomized at the start of the maintenance period. Subjects that received morphine in the titration period continued in the maintenance period on morphine. The trial includes a 2 week titration phase starting with either 45 mg Morphine Sulfate Controlled Release (CR) twice daily or 100 mg tapentadol ER taken twice daily (bid). Based on effectiveness and side effects participants can up-titrate in steps of 50 mg Tapentadol ER or 15 mg Morphine Sulfate CR to a maximal dose of 250 mg Tapentadol ER bid or 90 mg Morphine Sulfate CR

twice daily respectively. If subjects meet the stabilization 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.

Assessments of pain relief, defined as a responder include the pain intensity numeric rating scale (NRS). The Patient Global Impression of Change scale (PGIC) will also be used as a secondary efficacy endpoint. Safety evaluations include monitoring of adverse events, physical examinations, and clinical laboratory tests. Venous blood samples will be collected for the determination of serum concentrations of tapentadol.

Conditions

Conditions: Pain
Neoplasm
Cancer

Keywords: Chronic Tumor Related Pain
Analgesic
Tapentadol Extended Release
Morphine Sulfate Controlled Release
Pain assessment
Placebo

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 3

Intervention Model: Parallel Assignment

Number of Arms: 3

Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)

Allocation: Randomized

Endpoint Classification: Efficacy Study

Enrollment: 136 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Placebo Comparator: Matching Placebo Oral Tapentadol 100 mg to 250 mg twice daily. Followed by matching placebo in the maintenance (i.e. randomized withdrawal phase).	Drug: Matching Placebo in the Maintenance Phase after Tapentadol in the Titration Phase

Arms	Assigned Interventions
	Participant randomized to placebo in the maintenance phase received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off of the tapentadol dose they had received in the titration period. From the fourth day of the maintenance period onwards they received placebo twice daily.
Active Comparator: Morphine Controlled Release Oral Morphine 45 mg to 90 mg twice daily.	Drug: Morphine in the Maintenance Phase Participant started the trials with 45 mg morphine controlled release twice daily. Upward titration could then occur at a minimum of 3-day intervals in increments of 15 mg morphine twice daily. The maximum dose of morphine controlled release was 90 mg twice daily. Downward titration (but not below 45 mg twice daily) was permitted. In the maintenance phase participants continued on the dose level established in titration phase. Participants randomized to the morphine arm remained on morphine if they qualified for the maintenance phase of the study. The participants were maintained on the dose established at the end of the titration phase. The adverse events listed were documented in the maintenance phase. Other Names: • MS Contin overencapsulated for blinding Drug: Morphine in the Titration Phase After signing informed consent eligible subjects were randomized to receive morphine controlled release. The oral medication was taken twice daily, morning and evening every 12 hours (with a minimum of 6 hours between doses). Participant started the trials with 45 mg morphine controlled release twice daily. Upward titration could then occur at a minimum of 3-day intervals in increments of 15 mg morphine twice daily. The maximum dose of morphine controlled release was 90 mg twice daily. Downward titration (but not below 45 mg twice daily) was permitted.
Experimental: Tapentadol Extended Release Oral Tapentadol 100 mg to 250 mg twice daily.	Drug: Tapentadol in the Titration Phase Other Names: • Palexia • Nucynta Drug: Tapentadol in the Maintenance Phase The participants re-randomized to receive tapentadol prolonged release in the maintenance phase were maintained on the dose established in the titration phase.

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- A signed informed consent document.
- Male and non-pregnant, non-lactating female subjects.
- Female subjects must be post menopausal, surgically sterile, or practicing an effective method of birth control and continue to do so throughout the trial.
- At least 18 years of age.
- Have chronic malignant tumor-related pain
- Are opioid-naïve or have been pretreated with an equianalgesic dose range equivalent of up to 160 mg oral morphine per day and are dissatisfied with prior treatment.
- Have a mean pain intensity of at least 5 points on an 11-point Numeric Rating Scale (where 0 indicates no pain and 10 indicates worst possible pain).
- Have an expected course of the disease such that the pain that will permit compliance with the trial protocol over the entire trial period.

Exclusion Criteria:

- Have a life-long history of seizure disorder or epilepsy.
- Have had any of the following within one year: mild/moderate traumatic brain injury, stroke, and transient ischemic attack.
- Have had severe traumatic brain injury within 15 years (consisting of ≥ 1 of the following: brain contusion, intracranial hematoma, and either unconsciousness or post-traumatic amnesia lasting for more than 24 hours) or residual sequelae suggesting transient changes in consciousness.
- Have a known history and/or presence of cerebral metastases.
- Have moderately or severely impaired hepatic function.
- Have laboratory values reflecting inadequate hepatic function.
- Have thrombopenia, leucopenia or hypercalcemia
- Have severely impaired renal function.
- Having uncontrolled hypertension
- Having clinically relevant history of hypersensitivity, allergy or contraindications to morphine or any of the excipients.
- Have chronic hepatitis B or hepatitis C, or Human Immunodeficiency Virus (HIV).
- Subjects currently undergoing the following concomitant therapy: radiotherapy, pain inducing chemotherapy, anti-parkinsonian drugs, neuroleptics, monoamine oxidase inhibitors, serotonin norepinephrine re-uptake inhibitors (SNRI) or any other analgesic therapy than investigational medication or rescue medication during the trial. Selective serotonin re-uptake inhibitor (SSRI) treatments are allowed if taken for at least 30 days before the screening period of the trial at an unchanged dose.

Contacts/Locations

Study Officials: P. Poulain, Dr.
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Locations: United States, Florida
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056005
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380012
Donetsk, Ukraine, 83092

380002
Kharkiv, Ukraine, 61070

380008
Kharkiv, Ukraine, 61024

380001
Kiev, Ukraine, 61070

380013
Kiev, Ukraine, 01601

380009
Lviv, Ukraine, 79031

380010
Poltava, Ukraine, 36011

References

Citations:

Links:

Study Data/Documents:

Participant Flow

Recruitment Details	First participant in was enrolled on 29 June 2007 and the Last participant out was on the 02 February 2009. In general this was an out-patient study subject to country specific regulations.
Pre-Assignment Details	Eligible participants were required to stop their previous analgesic [pain treatment] therapy at randomization. 136 participants consented. 43 participants were not eligible for randomization to tapentadol extended release or morphine controlled release at baseline. 93 participants started the titration period.

Reporting Groups

	Description
Morphine (Maintenance Phase)	Participants in the maintenance phase continued on the dose level established in titration phase, i.e. 45 mg to 90 mg twice daily.
Tapentadol (Maintenance Phase)	Participants re-randomized to tapentadol prolonged release in the maintenance phase continued on the dose level established at the end of the titration phase. Oral tapentadol 100 mg to 250 mg twice daily.
Matching Placebo (Maintenance Phase)	Participants were re-randomized to placebo after being on tapentadol in the titration phase. At the start of this phase participants received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off of the tapentadol dose they had received in the titration period. From the fourth day of the maintenance period onwards they received placebo twice daily.
Tapentadol (Titration Phase)	After signing informed consent eligible participants were randomized to receive tapentadol extended release. Oral tapentadol 100 mg up to 250 mg twice daily. The oral medication was taken twice daily, morning and evening every 12 hours (with a minimum of 6 hours between doses).
Morphine (Titration Phase)	After signing informed consent eligible participants were randomized to receive morphine controlled release. The oral medication was taken twice daily starting at 45 mg up to 90 mg twice daily, morning and evening every 12 hours (with a minimum of 6 hours between doses).

Titration Phase

	Morphine (Maintenance Phase)	Tapentadol (Maintenance Phase)	Matching Placebo (Maintenance Phase)	Tapentadol (Titration Phase)	Morphine (Titration Phase)
Started	0	0	0	62	31
Completed	0	0	0	32	19
Not Completed	0	0	0	30	12
Adverse Event	0	0	0	8	3

	Morphine (Maintenance Phase)	Tapentadol (Maintenance Phase)	Matching Placebo (Maintenance Phase)	Tapentadol (Titration Phase)	Morphine (Titration Phase)
Death	0	0	0	2	0
Lack of Efficacy	0	0	0	10	1
Protocol Violation	0	0	0	0	1
Withdrawal by Subject	0	0	0	3	4
Underlying disease and therapy required	0	0	0	7	3

Maintenance Phase

	Morphine (Maintenance Phase)	Tapentadol (Maintenance Phase)	Matching Placebo (Maintenance Phase)	Tapentadol (Titration Phase)	Morphine (Titration Phase)
Started	18 [1]	15 [2]	14 [3]	0 [4]	0 [5]
Did Not Qualify for Maintenance Phase	0	0	0	3	1
Completed	12	10	6	0	0
Not Completed	6	5	8	0	0
Adverse Event	2	2	3	0	0
Death	2	0	1	0	0
Lack of Efficacy	2	1	1	0	0
Withdrawal by Subject	0	0	1	0	0
underlying disease and therapy required	0	2	2	0	0

[1] 18 of the 19 morphine participants continued with morphine in the maintenance phase.
[2] 15 of 32 tapentadol titration participants continued with tapentadol in the maintenance phase
[3] 14 of 32 tapentadol titration participants were treated with placebo in the maintenance phase.
[4] 29 of 32 participants were treated in the maintenance phase either with placebo or tapentadol
[5] 18 of 19 participants completing the morphine titration phase were continued on morphine.

Baseline Characteristics

Analysis Population Description

Safety Analysis Set. The information is correct for each treatment arm. The demographic details for the total population is for the 93 participants that started treatment in the titration phase of the trial.

The tapentadol titration population was subject to a randomized withdrawal-trial design.

Reporting Groups

	Description
Tapentadol (Titration Phase)	After signing informed consent eligible participants were randomized to receive tapentadol extended release. Oral tapentadol 100 mg to 250 mg twice daily. The oral medication was taken twice daily, morning and evening every 12 hours (with a minimum of 6 hours between doses).
Morphine (Titration Phase)	After signing informed consent eligible subjects were randomized to receive morphine controlled release. The oral medication was taken twice daily starting at 45 mg up to 90 mg twice daily, morning and evening every 12 hours (with a minimum of 6 hours between doses).

Baseline Measures

	Tapentadol (Titration Phase)	Morphine (Titration Phase)	Total
Number of Participants	62	31	93
Age, Continuous [units: years] Mean (Standard Deviation)			
Titration Phase (n=62, 31)	62.4 (12.51)	60.6 (11.77)	61.8 (12.23)
Morphine Maintenance (n=0, 18)	NA (NA) [1]	58.4 (12.65)	58.4 (12.65)
Tapentadol Maintenance (n=15, 0)	63.5 (9.34)	NA (NA) [2]	63.5 (9.34)
Placebo Maintenance (n=14, 0)	61.0 (12.93)	NA (NA) [2]	61.0 (12.93)
Gender, Customized [units: participants]			
Female (Titration)	35	12	47
Male (Titration)	27	19	46
Female (Morphine (Maintenance)	0	8	8

	Tapentadol (Titration Phase)	Morphine (Titration Phase)	Total
Male (Morphine Maintenance)	0	10	10
Female (Tapentadol Maintenance)	9	0	9
Male (Tapentadol Maintenance)	6	0	6
Female (Placebo Maintenance)	8	0	8
Male (Placebo Maintenance)	6	0	6
Race (NIH/OMB) [units: participants]			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	41	19	60
More than one race	0	0	0
Unknown or Not Reported	21	11	32
Region of Enrollment [units: participants]			
France	5	0	5
United States	3	4	7
Argentina	14	7	21
Ukraine	16	5	21
Chile	18	9	27
Latvia	6	6	12

[1] No participants from the Tapentadol Titration in this Arm.

[2] No participants from the Morphine Titration in this Arm.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Responder Rates in Maintenance Period
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 30 mg of rescue medication per day on average in the 28 day (excluding the first 3 days) 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 fails to meet at least 1 of the 3 criteria is not counted as a responder.
Time Frame	End of the 4 week Maintenance Phase (Day 43)
Safety Issue?	No

Analysis Population Description

Full Analysis Set. Number of participants with data available.

Reporting Groups

	Description
Morphine (Maintenance Phase)	Participants in the maintenance phase continued on the dose level established in titration phase, i.e. 45 mg to 90 mg twice daily.
Tapentadol (Maintenance Phase)	Participants re-randomized to tapentadol prolonged release in the maintenance phase continued on the dose level established at the end of the titration phase. Oral tapentadol 100 mg to 250 mg twice daily.
Matching Placebo (Maintenance Phase)	Participants were re-randomized to placebo after being on tapentadol in the titration phase. At the start of this phase participants received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off of the tapentadol dose they had received in the titration period. From the fourth day of the maintenance period onwards they received placebo twice daily.

Measured Values

	Morphine (Maintenance Phase)	Tapentadol (Maintenance Phase)	Matching Placebo (Maintenance Phase)
Number of Participants Analyzed	18	15	14
Responder Rates in Maintenance Period [units: participants]	6	8	3

2. Secondary Outcome Measure:

Measure Title	Patient Global Impression of Change (PGIC)
Measure Description	The Patient Global Impression of Change (PGIC) is an instrument where the participant indicates their perceived change at the end of a treatment phase. The overall participant status assessed using Patient Global Impression of Change (PGIC) self-assessment questionnaire which was used by participants to report on 7 categories listed as follows; Very Much Improved, Much Improved, Minimally Improved, No Change, Minimally Worse, Much Worse and Very Much Worse in tapentadol and morphine at Day 15 (Start of Maintenance Phase) and repeated in participants completing the Maintenance Phase in the Matching Placebo, Tapentadol and Morphine (Day 43).
Time Frame	Day 15 corresponds with PGIC at end of titration phase; Day 43 corresponds with PGIC at end of maintenance phase
Safety Issue?	No

Analysis Population Description

Full Analysis Set. Number of participants with data available.

Reporting Groups

	Description
Morphine (Maintenance Phase)	Participants in the maintenance phase continued on the dose level established in titration phase, i.e. 45 mg to 90 mg twice daily.
Tapentadol (Maintenance Phase)	Participants re-randomized to tapentadol prolonged release in the maintenance phase continued on the dose level established at the end of the titration phase. Oral tapentadol 100 mg to 250 mg twice daily.
Matching Placebo (Maintenance Phase)	Participants were re-randomized to placebo after being on tapentadol in the titration phase. At the start of this phase participants received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off of the tapentadol dose they had received in the titration period. From the fourth day of the maintenance period onwards they received placebo twice daily.
Tapentadol (Titration Phase)	After signing informed consent eligible participants were randomized to receive tapentadol extended release. Oral tapentadol 100 mg to 250 mg twice daily. The oral medication was taken twice daily, morning and evening every 12 hours (with a minimum of 6 hours between doses).
Morphine (Titration Phase)	After signing informed consent eligible subjects were randomized to receive morphine controlled release. The oral medication was taken twice daily starting at 45 mg up to 90 mg twice daily, morning and evening every 12 hours (with a minimum of 6 hours between doses).

Measured Values

	Morphine (Maintenance Phase)	Tapentadol (Maintenance Phase)	Matching Placebo (Maintenance Phase)	Tapentadol (Titration Phase)	Morphine (Titration Phase)
Number of Participants Analyzed	18	15	14	62	31
Patient Global Impression of Change (PGIC) [units: participants]					
Very Much Improved	1	0	0	0	0
Much Improved	3	8	2	5	1
Minimally Improved	4	4	4	8	4
No Change	4	1	1	3	2
Minimally Worse	0	1	0	4	0
Much Worse	1	1	2	2	0
Very Much Worse	0	0	0	0	0
Missing	5	0	5	40	24

Reported Adverse Events

Time Frame	Participants were to be treated for up to 42 days: Titration (14 days) and Maintenance Phase (up to 28 days).
Additional Description	More than one event might have occured in the same participant.

Reporting Groups

	Description
Morphine (Maintenance Phase)	Participants in the maintenance phase continued on the dose level established in titration phase, i.e. 45 mg to 90 mg twice daily.
Tapentadol (Maintenance Phase)	Participants re-randomized to tapentadol prolonged release in the maintenance phase continued on the dose level established at the end of the titration phase. Oral tapentadol 100 mg to 250 mg twice daily.

	Description
Matching Placebo (Maintenance Phase)	Participants were re-randomized to placebo after being on tapentadol in the titration phase. At the start of this phase participants received 100 mg tapentadol prolonged release twice daily for 3 days to taper them off of the tapentadol dose they had received in the titration period. From the fourth day of the maintenance period onwards they received placebo twice daily.
Tapentadol (Titration Phase)	After signing informed consent eligible participants were randomized to receive tapentadol extended release. Oral tapentadol 100 mg to 250 mg twice daily. The oral medication was taken twice daily, morning and evening every 12 hours (with a minimum of 6 hours between doses).
Morphine (Titration Phase)	After signing informed consent eligible subjects were randomized to receive morphine controlled release. The oral medication was taken twice daily starting at 45 mg up to 90 mg twice daily, morning and evening every 12 hours (with a minimum of 6 hours between doses).

Serious Adverse Events

	Morphine (Maintenance Phase)	Tapentadol (Maintenance Phase)	Matching Placebo (Maintenance Phase)	Tapentadol (Titration Phase)	Morphine (Titration Phase)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	4/18 (22.22%)	2/15 (13.33%)	4/14 (28.57%)	11/62 (17.74%)	4/31 (12.9%)
Blood and lymphatic system disorders					
Anemia [A] [1] †	0/18 (0%)	0/15 (0%)	1/14 (7.14%)	1/62 (1.61%)	0/31 (0%)
Gastrointestinal disorders					
Abdominal Pain [A] †	0/18 (0%)	0/15 (0%)	0/14 (0%)	1/62 (1.61%)	0/31 (0%)
Diarrhoea [A] †	0/18 (0%)	0/15 (0%)	0/14 (0%)	1/62 (1.61%)	0/31 (0%)
Dysphagia [A] †	0/18 (0%)	0/15 (0%)	1/14 (7.14%)	0/62 (0%)	0/31 (0%)
Intestinal Obstruction [A] †	0/18 (0%)	0/15 (0%)	0/14 (0%)	1/62 (1.61%)	0/31 (0%)
Nausea [A] †	1/18 (5.56%)	0/15 (0%)	0/14 (0%)	0/62 (0%)	0/31 (0%)
Vomiting [A] †	1/18 (5.56%)	0/15 (0%)	0/14 (0%)	1/62 (1.61%)	0/31 (0%)
General disorders					
Asthenia [A] †	0/18 (0%)	0/15 (0%)	0/14 (0%)	0/62 (0%)	1/31 (3.23%)
Chest Pain [A] †	0/18 (0%)	0/15 (0%)	0/14 (0%)	1/62 (1.61%)	0/31 (0%)

	Morphine (Maintenance Phase)	Tapentadol (Maintenance Phase)	Matching Placebo (Maintenance Phase)	Tapentadol (Titration Phase)	Morphine (Titration Phase)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Death [A] †	1/18 (5.56%)	0/15 (0%)	0/14 (0%)	1/62 (1.61%)	0/31 (0%)
Infections and infestations					
Pneumonia [A] †	0/18 (0%)	0/15 (0%)	0/14 (0%)	0/62 (0%)	2/31 (6.45%)
Pyelonephritis [A] †	1/18 (5.56%)	0/15 (0%)	0/14 (0%)	0/62 (0%)	0/31 (0%)
Injury, poisoning and procedural complications					
Hip Fracture [A] †	0/18 (0%)	0/15 (0%)	0/14 (0%)	1/62 (1.61%)	0/31 (0%)
Metabolism and nutrition disorders					
Diabetes Mellitus Inadequate Control [A] †	0/18 (0%)	0/15 (0%)	0/14 (0%)	1/62 (1.61%)	0/31 (0%)
Musculoskeletal and connective tissue disorders					
Back Pain [A] †	0/18 (0%)	0/15 (0%)	0/14 (0%)	1/62 (1.61%)	0/31 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Malignant Neoplasm Progression [A] †	1/18 (5.56%)	2/15 (13.33%)	2/14 (14.29%)	3/62 (4.84%)	1/31 (3.23%)
Psychiatric disorders					
Disorientation [A] †	0/18 (0%)	0/15 (0%)	0/14 (0%)	1/62 (1.61%)	0/31 (0%)
Mental Status Change [A] †	0/18 (0%)	0/15 (0%)	0/14 (0%)	1/62 (1.61%)	0/31 (0%)
Respiratory, thoracic and mediastinal disorders					
Respiratory Failure [A] †	0/18 (0%)	0/15 (0%)	0/14 (0%)	1/62 (1.61%)	0/31 (0%)
Vascular disorders					
Deep Vein Thrombosis [A] †	1/18 (5.56%)	0/15 (0%)	0/14 (0%)	0/62 (0%)	0/31 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 12.0

[1] The participant was initially in the tapentadol titration phase with the first episode of anemia. The participant was subsequently in the placebo maintenance treatment group. Participant was withdrawn. Outcome of the third event was fatal.

Other Adverse Events

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

	Morphine (Maintenance Phase)	Tapentadol (Maintenance Phase)	Matching Placebo (Maintenance Phase)	Tapentadol (Titration Phase)	Morphine (Titration Phase)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	12/18 (66.67%)	9/15 (60%)	7/14 (50%)	28/62 (45.16%)	17/31 (54.84%)
Cardiac disorders					
Tachycardia [A] †	0/18 (0%)	0/15 (0%)	1/14 (7.14%)	0/62 (0%)	0/31 (0%)
Ear and labyrinth disorders					
Vertigo [A] †	1/18 (5.56%)	0/15 (0%)	1/14 (7.14%)	4/62 (6.45%)	0/31 (0%)
Gastrointestinal disorders					
Abdominal Pain [A] †	1/18 (5.56%)	0/15 (0%)	0/14 (0%)	1/62 (1.61%)	0/31 (0%)
Abdominal Pain Upper [A] †	0/18 (0%)	1/15 (6.67%)	1/14 (7.14%)	2/62 (3.23%)	0/31 (0%)
Constipation [A] †	2/18 (11.11%)	1/15 (6.67%)	0/14 (0%)	6/62 (9.68%)	3/31 (9.68%)
Diarrhoea [A] †	3/18 (16.67%)	1/15 (6.67%)	0/14 (0%)	2/62 (3.23%)	0/31 (0%)
Dry Mouth [A] †	0/18 (0%)	0/15 (0%)	1/14 (7.14%)	2/62 (3.23%)	1/31 (3.23%)
Flatulence [A] †	0/18 (0%)	0/15 (0%)	1/14 (7.14%)	2/62 (3.23%)	0/31 (0%)
Lip Oedema [A] †	0/18 (0%)	1/15 (6.67%)	0/14 (0%)	0/62 (0%)	0/31 (0%)
Nausea [A] †	2/18 (11.11%)	1/15 (6.67%)	2/14 (14.29%)	7/62 (11.29%)	4/31 (12.9%)
Vomiting [A] †	2/18 (11.11%)	2/15 (13.33%)	1/14 (7.14%)	9/62 (14.52%)	2/31 (6.45%)
General disorders					
Asthenia [A] †	1/18 (5.56%)	0/15 (0%)	0/14 (0%)	2/62 (3.23%)	2/31 (6.45%)
Chills [A] †	1/18 (5.56%)	0/15 (0%)	0/14 (0%)	0/62 (0%)	1/31 (3.23%)
Oedema [A] †	0/18 (0%)	1/15 (6.67%)	0/14 (0%)	0/62 (0%)	1/31 (3.23%)
Pyrexia [A] †	0/18 (0%)	0/15 (0%)	1/14 (7.14%)	3/62 (4.84%)	1/31 (3.23%)

	Morphine (Maintenance Phase)	Tapentadol (Maintenance Phase)	Matching Placebo (Maintenance Phase)	Tapentadol (Titration Phase)	Morphine (Titration Phase)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Thirst [A] †	1/18 (5.56%)	0/15 (0%)	0/14 (0%)	0/62 (0%)	1/31 (3.23%)
Infections and infestations					
Bronchitis [A] †	1/18 (5.56%)	0/15 (0%)	0/14 (0%)	2/62 (3.23%)	0/31 (0%)
Pneumonia [A] †	0/18 (0%)	0/15 (0%)	0/14 (0%)	0/62 (0%)	2/31 (6.45%)
Rhinitis [A] †	0/18 (0%)	1/15 (6.67%)	0/14 (0%)	0/62 (0%)	0/31 (0%)
Urinary Tract Infection [A] †	0/18 (0%)	0/15 (0%)	1/14 (7.14%)	2/62 (3.23%)	0/31 (0%)
Investigations					
Blood Lactate Dehydrogenase Increased [A] †	0/18 (0%)	0/15 (0%)	0/14 (0%)	0/62 (0%)	2/31 (6.45%)
Metabolism and nutrition disorders					
Anorexia [A] †	2/18 (11.11%)	0/15 (0%)	1/14 (7.14%)	2/62 (3.23%)	1/31 (3.23%)
Hypokalaemia [A] †	0/18 (0%)	0/15 (0%)	1/14 (7.14%)	0/62 (0%)	0/31 (0%)
Musculoskeletal and connective tissue disorders					
Arthralgia [A] †	1/18 (5.56%)	0/15 (0%)	0/14 (0%)	0/62 (0%)	1/31 (3.23%)
Back Pain [A] †	1/18 (5.56%)	1/15 (6.67%)	0/14 (0%)	1/62 (1.61%)	0/31 (0%)
Torticollis [A] †	0/18 (0%)	1/15 (6.67%)	0/14 (0%)	0/62 (0%)	0/31 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Malignant Neoplasm Progression [A] †	1/18 (5.56%)	0/15 (0%)	0/14 (0%)	0/62 (0%)	1/31 (3.23%)
Nervous system disorders					
Dizziness [A] †	0/18 (0%)	0/15 (0%)	1/14 (7.14%)	4/62 (6.45%)	1/31 (3.23%)
Hemiparesis [A] †	0/18 (0%)	1/15 (6.67%)	0/14 (0%)	0/62 (0%)	0/31 (0%)
Somnolence [A] †	0/18 (0%)	0/15 (0%)	0/14 (0%)	2/62 (3.23%)	2/31 (6.45%)
Tremor [A] †	1/18 (5.56%)	0/15 (0%)	0/14 (0%)	2/62 (3.23%)	0/31 (0%)

	Morphine (Maintenance Phase)	Tapentadol (Maintenance Phase)	Matching Placebo (Maintenance Phase)	Tapentadol (Titration Phase)	Morphine (Titration Phase)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Psychiatric disorders					
Depression [A] †	0/18 (0%)	1/15 (6.67%)	0/14 (0%)	0/62 (0%)	0/31 (0%)
Insomnia [A] †	0/18 (0%)	0/15 (0%)	2/14 (14.29%)	5/62 (8.06%)	0/31 (0%)
Nervousness [A] †	0/18 (0%)	0/15 (0%)	1/14 (7.14%)	0/62 (0%)	1/31 (3.23%)
Renal and urinary disorders					
Choluria [A] †	1/18 (5.56%)	0/15 (0%)	0/14 (0%)	0/62 (0%)	0/31 (0%)
Respiratory, thoracic and mediastinal disorders					
Dyspnoea [A] †	0/18 (0%)	1/15 (6.67%)	0/14 (0%)	2/62 (3.23%)	1/31 (3.23%)
Haemoptysis [A] †	1/18 (5.56%)	0/15 (0%)	0/14 (0%)	0/62 (0%)	0/31 (0%)
Rhinorrhoea [A] †	1/18 (5.56%)	0/15 (0%)	0/14 (0%)	0/62 (0%)	0/31 (0%)
Skin and subcutaneous tissue disorders					
Pruritus [A] †	0/18 (0%)	0/15 (0%)	0/14 (0%)	1/62 (1.61%)	3/31 (9.68%)
Skin Lesion [A] †	1/18 (5.56%)	0/15 (0%)	0/14 (0%)	0/62 (0%)	0/31 (0%)
Vascular disorders					
Hypotension [A] †	0/18 (0%)	0/15 (0%)	1/14 (7.14%)	0/62 (0%)	0/31 (0%)
Orthostatic Hypotension [A] †	0/18 (0%)	0/15 (0%)	1/14 (7.14%)	3/62 (4.84%)	0/31 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 12.0

Limitations and Caveats

Early termination, due to a recall of the morphine rescue medication and issues regarding supply of an alternative, lead to only 93 participants out of the 573 planned (16%) being available for analysis. The data should be interpreted with caution.

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 and the Sponsor's designee 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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