Clinical trial results:
Relative bioavailability trial to investigate the pharmacokinetics of tapentadol following the administration of 3 prototype tapentadol 25 mg prolonged release (PR) granule formulations compared to a Palexia® PR 25 mg tablet in healthy adult subjects.

Summary

EudraCT number	2012-005499-33
Trial protocol	DE
Global end of trial date	15 June 2015

Results information

Result version number	v1 (current)
This version publication date	04 June 2016
First version publication date	04 June 2016

Trial information

Trial identification

Sponsor protocol code	HP5503-88

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1159-4436

Notes:

Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr. 6, Aachen, Germany, 52099
Public contact	Grünenthal Clinical Trial Helpdesk, Grünenthal GmbH, +49 241569 3223, Clinical-Trials@grunenthal.com
Scientific contact	Grünenthal Clinical Trial Helpdesk, Grünenthal GmbH, +49 241569 3223, Clinical-Trials@grunenthal.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000325-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 June 2015
Global end of trial reached?	Yes
Global end of trial date	15 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to assess the pharmacokinetics and relative bioavailability of tapentadol following administration of 3 prototype tapentadol PR granule formulations (test formulations) each containing 25 mg tapentadol, compared to 1 tablet of Palexia® PR 25 mg (reference formulation).

This trial was conducted in two parts:
Part 1 in fasted condition with a 4-treatment, 4-period crossover design
Part 2 in fed condition with a 3-treatment, 3-period crossover design
Each part includes a different set of male subjects.

No endpoint was defined for this trial.
The main pharmacokinetic target parameters were Cmax and AUC0-t for tapentadol. In addition, the analyses of AUC for tapentadol will be reported.

Protection of trial subjects:

The trial was conducted according to ICH-GCP guidelines, the applicable local law, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki.
National regulations and national authorization was obtained.

Background therapy:

Any prescribed or non-prescribed medications (excluding topical medications or nasal sprays without systemic effect) used on a regular basis within 14 days and Monoamine oxidase inhibitors used within 21 days before the Enrollment Visit were forbidden.

Concomitant medications allowed during the trial were:
• Paracetamol (e.g., for headache).
• Treatments for nausea or vomiting, according to standard medical practice.
• Topical medications without systemic effect.
• Nasal sprays without systemic effect.
• Naloxone, which may be administered as rescue medication for clinically significant respiratory depression requiring emergency medical intervention.

Forbidden concomitant medication during the trial were:
• Regular use of any prescribed or non-prescribed medications (excluding topical medications or nasal sprays without systemic effect) after the Enrollment Visit.

Evidence for comparator:

PALEXIA® prolonged release is indicated for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics.
The dosing regimen should be individualised according to the severity of pain being treated, the previous treatment experience and the ability to monitor the patient.

Actual start date of recruitment	27 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	48
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial started on 27 Jan 2015 with the first subject in (in Part 1) and was completed on 15 Jun 2015 with the last subject out (from Part 2).
Each part of the trial included a different set of 24 healthy male subjects.

Pre-assignment

Screening details:

A total of 114 subjects signed an informed consent form and were involved in /undergoing the enrollment visit procedure. 66 subjects dropped out before allocation to treatment.

Pre-assignment period milestones

Number of subjects started	114[1]
Number of subjects completed	48

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Elevated systolic blood pressure and heart rate: 1
Reason: Number of subjects	Inclusion criteria not met/exclusion criteria met: 48
Reason: Number of subjects	Private reason: 8
Reason: Number of subjects	Supernumerous subject: 9

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 114 subjects signed an informed consent = Pre-assignment period.
A total of 48 healthy Caucasian male subjects aged between 18 years and 55 years inclusive, with 24 subjects in Part 1 and Part 2, respectively, entered the 'Overall Trial' period and received IMP (Investigational medicinal product)
Pharmacokinetic data was obtained for all of these subjects.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1_in fasted condition

Arm description:

Part 1 had a 4-treatment, 4-period crossover single dose design to assess the relative bioavailability of 3 prototype tapentadol prolonged-release (PR) granule formulations (test formulations) compared to 1 tablet of Palexia® prolonged-release (PR) 25 mg (reference formulation) under fasted condition.

This arm includes all subjects allocated to treatment sequences in Part 1 with at least 1 IMP administration.

The treatment codes were defined as followed:
C – Palexia® 25 mg prolonged-release tablet
T1 – Tapentadol 25 mg prolonged-release granules 15% coating level
T2 – Tapentadol 25 mg prolonged-release granules 20% coating level
T3 – Tapentadol 25 mg prolonged-release granules 25% coating level

Arm type	Experimental

Investigational medicinal product name	Tapentadol 25 mg prolonged-release granules 15% coating level
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose of Tapentadol PR 25 mg granules with coating 15% under fasted condition.

Investigational medicinal product name	Tapentadol 25 mg prolonged-release granules 20% coating level
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose of Tapentadol PR 25 mg granules with coating 20% under fasted condition.

Investigational medicinal product name	Tapentadol 25 mg prolonged-release granules 25% coating level
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose of Tapentadol PR 25 mg granules with coating 25% under fasted condition.

Investigational medicinal product name	Palexia® 25 mg prolonged-release tablet
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose of Palexia® PR 25 mg tablet under fasted condition.

Arm title	Part 2_in fed condition

Arm description:

Part 2 had a 3-treatment, 3-period crossover single dose design to assess the relative bioavailability of 2 prototype tapentadol prolonged-release PR granule formulations (test formulations) compared to 1 tablet of Palexia® PR 25 mg (reference formulation) under fed condition.
This arm includes all subjects allocated to treatment sequences in Part 2 with at least 1 IMP administration.

The treatment codes were defined as followed:
C – Palexia® 25 mg prolonged-release tablet
T1 – Tapentadol 25 mg prolonged-release granules 15% coating level
T2 – Tapentadol 25 mg prolonged-release granules 20% coating level

Arm type	Experimental
Investigational medicinal product name	Tapentadol 25 mg prolonged-release granules 15% coating level
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose of Tapentadol PR 25 mg granules with coating 15% under fed condition.

Investigational medicinal product name	Tapentadol 25 mg prolonged-release granules 20% coating level
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose of Tapentadol PR 25 mg granules with coating 20% under fed condition.

Investigational medicinal product name	Palexia® 25 mg prolonged-release tablet
Investigational medicinal product code	CG5503
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single oral dose of Palexia® PR 25 mg tablet under fed condition.

Number of subjects in period 1	Part 1_in fasted condition	Part 2_in fed condition
Started	24	24
Completed	23	23
Not completed	1	1
Private reason	1	-
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part 1_in fasted condition

Reporting group description:

Part 1 had a 4-treatment, 4-period crossover single dose design to assess the relative bioavailability of 3 prototype tapentadol prolonged-release (PR) granule formulations (test formulations) compared to 1 tablet of Palexia® prolonged-release (PR) 25 mg (reference formulation) under fasted condition.

This arm includes all subjects allocated to treatment sequences in Part 1 with at least 1 IMP administration.

The treatment codes were defined as followed:
C – Palexia® 25 mg prolonged-release tablet
T1 – Tapentadol 25 mg prolonged-release granules 15% coating level
T2 – Tapentadol 25 mg prolonged-release granules 20% coating level
T3 – Tapentadol 25 mg prolonged-release granules 25% coating level

Reporting group title	Part 2_in fed condition

Reporting group description:

Part 2 had a 3-treatment, 3-period crossover single dose design to assess the relative bioavailability of 2 prototype tapentadol prolonged-release PR granule formulations (test formulations) compared to 1 tablet of Palexia® PR 25 mg (reference formulation) under fed condition.
This arm includes all subjects allocated to treatment sequences in Part 2 with at least 1 IMP administration.

The treatment codes were defined as followed:
C – Palexia® 25 mg prolonged-release tablet
T1 – Tapentadol 25 mg prolonged-release granules 15% coating level
T2 – Tapentadol 25 mg prolonged-release granules 20% coating level

Reporting group values	Part 1_in fasted condition	Part 2_in fed condition	Total
Number of subjects	24	24	48
Age categorical Units: Subjects			
Adults (18-64 years)	24	24	48
Age continuous Units: years			
arithmetic mean	41	41	
standard deviation	± 9.5	± 10.1	-
Gender categorical Units: Subjects			
Male	24	24	48
Height Units: cm			
arithmetic mean	177.4	177	
standard deviation	± 6.9	± 5.5	-
Weight Units: kg			
arithmetic mean	80.95	81.74	
standard deviation	± 8.32	± 7.59	-
BMI Units: kg/m**2			
arithmetic mean	25.73	26.11	
standard deviation	± 2.17	± 2.17	-

End points

End points reporting groups

Reporting group title	Part 1_in fasted condition

Reporting group description:

Part 1 had a 4-treatment, 4-period crossover single dose design to assess the relative bioavailability of 3 prototype tapentadol prolonged-release (PR) granule formulations (test formulations) compared to 1 tablet of Palexia® prolonged-release (PR) 25 mg (reference formulation) under fasted condition.

This arm includes all subjects allocated to treatment sequences in Part 1 with at least 1 IMP administration.

The treatment codes were defined as followed:
C – Palexia® 25 mg prolonged-release tablet
T1 – Tapentadol 25 mg prolonged-release granules 15% coating level
T2 – Tapentadol 25 mg prolonged-release granules 20% coating level
T3 – Tapentadol 25 mg prolonged-release granules 25% coating level

Reporting group title	Part 2_in fed condition

Reporting group description:

Part 2 had a 3-treatment, 3-period crossover single dose design to assess the relative bioavailability of 2 prototype tapentadol prolonged-release PR granule formulations (test formulations) compared to 1 tablet of Palexia® PR 25 mg (reference formulation) under fed condition.
This arm includes all subjects allocated to treatment sequences in Part 2 with at least 1 IMP administration.

The treatment codes were defined as followed:
C – Palexia® 25 mg prolonged-release tablet
T1 – Tapentadol 25 mg prolonged-release granules 15% coating level
T2 – Tapentadol 25 mg prolonged-release granules 20% coating level

Subject analysis set title	PK Set 1_fasting_15% coating (T1)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received a single dose of Tapentadol PR 25 mg granules with coating 15% under fasted condition.
The Pharmacokinetic Set 1 (PK Set 1) comprised all subjects providing sufficient data, i.e., at least Cmax or AUC0-t, to compare at least 1 of the test formulations with the reference formulation in Part 1. They were included in the primary pharmacokinetic analyses of Part 1.

Subject analysis set title	PK Set 1_fasting_20% coating (T2)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received a single dose of Tapentadol PR 25 mg granules with coating 20% under fasted condition.
The Pharmacokinetic Set 1 (PK Set 1) comprised all subjects providing sufficient data, i.e., at least Cmax or AUC0-t, to compare at least 1 of the test formulations with the reference formulation in Part 1. They were included in the primary pharmacokinetic analyses of Part 1.

Subject analysis set title	PK Set 1_fasting_25% coating (T3)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received a single dose of Tapentadol PR 25 mg granules with coating 25% under fasted condition.
The Pharmacokinetic Set 1 (PK Set 1) comprised all subjects providing sufficient data, i.e., at least Cmax or AUC0-t, to compare at least 1 of the test formulations with the reference formulation in Part 1. They were included in the primary pharmacokinetic analyses of Part 1.

Subject analysis set title	PK Set 2_fed_15% coating (T1)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received a single dose of Tapentadol PR 25 mg granules with coating 15% under fed condition.
The Pharmacokinetic Set 2 (PK Set 2) comprised all subjects providing sufficient data, i.e., at least Cmax or AUC0-t, to compare at least 1 of the test formulations with the reference formulation in Part 2. They were included in the primary pharmacokinetic analyses of Part 2.

Subject analysis set title	PK Set 2_fed_20% coating (T2)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received a single dose of Tapentadol PR 25 mg granules with coating 20% under fed condition.
The Pharmacokinetic Set 2 (PK Set 2) comprised all subjects providing sufficient data, i.e., at least Cmax or AUC0-t, to compare at least 1 of the test formulations with the reference formulation in Part 2. They were included in the primary pharmacokinetic analyses of Part 2.

Subject analysis set title	PK Set 1_fasting _Palexia® PR 25 mg tablet (C)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received a single dose of Palexia® PR 25 mg tablet under fasted condition.
The Pharmacokinetic Set 1 (PK Set 1) comprised all subjects providing sufficient data, i.e., at least Cmax or AUC0-t, to compare at least 1 of the test formulations with the reference formulation in Part 1. They were included in the primary pharmacokinetic analyses of Part 1.

Subject analysis set title	PK Set 2_fed_Palexia® PR 25 mg tablet (C)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received a single dose of Palexia® PR 25 mg tablet under fed condition.
The Pharmacokinetic Set 2 (PK Set 2) comprised all subjects providing sufficient data, i.e., at least Cmax or AUC0-t, to compare at least 1 of the test formulations with the reference formulation in Part 2. They were included in the primary pharmacokinetic analyses of Part 2.

Primary: No endpoints have been defined for this trial.

End point title	No endpoints have been defined for this trial.[1]

End point description:

End point type	Primary

End point timeframe:

No endpoints have been defined for this trial.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: In HP5503-88 (exploratory Phase I trials) endpoints were specified using PK variables. The primary and secondary trial objectives were defined and appropriate analysis of data reported in pre-defined endpoint sections.

End point values	Part 1_in fasted condition	Part 2_in fed condition		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: not applicable	24	24		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Primary statistical analysis of pharmacokinetic parameters_Cmax

End point title	Primary statistical analysis of pharmacokinetic parameters_Cmax

End point description:

Pharmacokinetic analysis of Cmax of tapentadol.
The Pharmacokinetic Sets (PK Set) comprised all subjects providing sufficient data, i.e., at least Cmax or

AUC0-t, to compare at least 1 of the test formulations with the reference formulation for the Pharmacokinetic Sets of Part 1 (PK Set 1) and Part 2 (PK Set 2), respectively.

Note:
Due to the crossover design, the same subjects received different treatments within each part.
The number of subjects included in the treatment comparisons of Cmax is 23 in Part 1 and 23 in Part 2 instead of the automatically calculated 46.

End point type	Other pre-specified

End point timeframe:

Blood for pharmacokinetic analysis was taken up to 32 hours after IMP administration.

End point values	PK Set 1_fasting_15% coating (T1)	PK Set 1_fasting_20% coating (T2)	PK Set 1_fasting_25% coating (T3)	PK Set 2_fed_15% coating (T1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	23	23	23
Units: ng/mL				
least squares mean (confidence interval 90%)	4.9244 (4.7032 to 5.1559)	4.7657 (4.5517 to 4.9898)	4.3973 (4.1999 to 4.6041)	9.9601 (9.4558 to 10.4913)

End point values	PK Set 2_fed_20% coating (T2)	PK Set 1_fasting _Palexia® PR 25 mg tablet (C)	PK Set 2_fed_Palexia ® PR 25 mg tablet (C)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	23	23	23	
Units: ng/mL				
least squares mean (confidence interval 90%)	8.3541 (7.9311 to 8.7997)	4.5882 (4.3821 to 4.8039)	9.8553 (9.3563 to 10.3809)	

Statistical analyses

Statistical analysis title	ANOVA_PK Set 1_T1/C_Cmax

Statistical analysis description:

The statistical analysis of pharmacokinetic parameters was an analysis of variance (ANOVA) of the parameter Cmax in the Pharmacokinetic Set of Part 1 (PK Set 1).
The analysis has been performed using log transformed values. The ANOVA model was fitted to the data with Cmax as the dependent variable, and the effects due to treatment sequence group, period, treatment, and subjects nested within sequence as fixed effects.

Comparison groups	PK Set 1_fasting_15% coating (T1) v PK Set 1_fasting _Palexia® PR 25 mg tablet (C)

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.0733
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.0058
upper limit	1.1453

Statistical analysis title	ANOVA_PK Set 1_T2/C_Cmax

Statistical analysis description:

The statistical analysis of pharmacokinetic parameters was an analysis of variance (ANOVA) of the parameter Cmax in the Pharmacokinetic Set of Part 1 (PK Set 1).
The analysis has been performed using log transformed values. The ANOVA model was fitted to the data with Cmax as the dependent variable, and the effects due to treatment sequence group, period, treatment, and subjects nested within sequence as fixed effects.

Comparison groups	PK Set 1_fasting_20% coating (T2) v PK Set 1_fasting _Palexia® PR 25 mg tablet (C)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.0387
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9734
upper limit	1.1084

Statistical analysis title	ANOVA_PK Set 1_T3/C_Cmax

Statistical analysis description:

The statistical analysis of pharmacokinetic parameters was an analysis of variance (ANOVA) of the parameter Cmax in the Pharmacokinetic Set of Part 1 (PK Set 1).
The analysis has been performed using log transformed values. The ANOVA model was fitted to the data with Cmax as the dependent variable, and the effects due to treatment sequence group, period, treatment, and subjects nested within sequence as fixed effects.

Comparison groups	PK Set 1_fasting_25% coating (T3) v PK Set 1_fasting _Palexia® PR 25 mg tablet (C)

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.9584
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8981
upper limit	1.0227

Statistical analysis title	ANOVA_PK Set 2_T1/C_Cmax

Statistical analysis description:

The statistical analysis of pharmacokinetic parameters was an analysis of variance (ANOVA) of the parameter Cmax in the Pharmacokinetic Set of Part 2 (PK Set 2).
The analysis has been performed using log transformed values. The ANOVA model was fitted to the data with Cmax as the dependent variable, and the effects due to treatment sequence group, period, treatment, and subjects nested within sequence as fixed effects.

Comparison groups	PK Set 2_fed_15% coating (T1) v PK Set 2_fed_Palexia® PR 25 mg tablet (C)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.0106
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9391
upper limit	1.0876

Statistical analysis title	ANOVA_PK Set 2_T2/C_Cmax

Statistical analysis description:

The statistical analysis of pharmacokinetic parameters was an analysis of variance (ANOVA) of the parameter Cmax in the Pharmacokinetic Set of Part 2 (PK Set 2).
The analysis has been performed using log transformed values. The ANOVA model was fitted to the data with Cmax as the dependent variable, and the effects due to treatment sequence group, period, treatment, and subjects nested within sequence as fixed effects.

Comparison groups	PK Set 2_fed_20% coating (T2) v PK Set 2_fed_Palexia® PR 25 mg tablet (C)

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.8477
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.7877
upper limit	0.9122

Other pre-specified: Primary statistical analysis of pharmacokinetic parameters_AUC0-t

End point title	Primary statistical analysis of pharmacokinetic parameters_AUC0-t

End point description:

Pharmacokinetic analysis of AUC0-t of tapentadol.
The Pharmacokinetic Sets (PK Set) comprised all subjects providing sufficient data, i.e., at least Cmax or AUC0-t, to compare at least 1 of the test formulations with the reference formulation for the Pharmacokinetic Sets of Part 1 (PK Set 1) and Part 2 (PK Set 2), respectively.

Note:
Due to the crossover design, the same subjects received different treatments within each part.
The number of subjects included in the treatment comparisons of AUC0-t is 23 in Part 1 and 23 in Part 2 instead of the automatically calculated 46.

End point type	Other pre-specified

End point timeframe:

Blood for pharmacokinetic analysis was taken up to 32 hours after IMP administration.

End point values	PK Set 1_fasting_15% coating (T1)	PK Set 1_fasting_20% coating (T2)	PK Set 1_fasting_25% coating (T3)	PK Set 2_fed_15% coating (T1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	23	23	23
Units: h·ng/mL				
least squares mean (confidence interval 90%)	58.5895 (56.5522 to 60.7002)	61.4336 (59.2974 to 63.6468)	64.6398 (62.3921 to 66.9685)	96.0943 (93.0071 to 99.284)

End point values	PK Set 2_fed_20% coating (T2)	PK Set 1_fasting _Palexia® PR 25 mg tablet (C)	PK Set 2_fed_Palexia ® PR 25 mg tablet (C)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	23	23	23	
Units: h·ng/mL				
least squares mean (confidence interval	91.2479	64.8975	101.264	

90%)	(88.3163 to 94.2767)	(62.6408 to 67.2355)	(98.0107 to 104.6253)

Statistical analyses

Statistical analysis title	ANOVA_PK Set 1_T1/C_AUC0-t

Statistical analysis description:

The statistical analysis of pharmacokinetic parameters was an analysis of variance (ANOVA) of the parameter AUC0-t in the Pharmacokinetic Set of Part 1 (PK set 1).
The analysis has been performed using log transformed values. The ANOVA model was fitted to the data with AUC0-t as the dependent variable, and the effects due to treatment sequence group, period, treatment, and subjects nested within sequence as fixed effects.

Comparison groups	PK Set 1_fasting_15% coating (T1) v PK Set 1_fasting _Palexia® PR 25 mg tablet (C)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.9028
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8587
upper limit	0.9491

Statistical analysis title	ANOVA_PK Set 1_T2/C_AUC0-t

Statistical analysis description:

The statistical analysis of pharmacokinetic parameters was an analysis of variance (ANOVA) of the parameter AUC0-t in the Pharmacokinetic Set of Part 1 (PK set 1).
The analysis has been performed using log transformed values. The ANOVA model was fitted to the data with AUC0-t as the dependent variable, and the effects due to treatment sequence group, period, treatment, and subjects nested within sequence as fixed effects.

Comparison groups	PK Set 1_fasting_20% coating (T2) v PK Set 1_fasting _Palexia® PR 25 mg tablet (C)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.9466
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9004
upper limit	0.9952

Statistical analysis title	ANOVA_PK Set 1_T3/C_AUC0-t

Statistical analysis description:

The statistical analysis of pharmacokinetic parameters was an analysis of variance (ANOVA) of the parameter AUC0-t in the Pharmacokinetic Set of Part 1 (PK set 1).
The analysis has been performed using log transformed values. The ANOVA model was fitted to the data with AUC0-t as the dependent variable, and the effects due to treatment sequence group, period, treatment, and subjects nested within sequence as fixed effects.

Comparison groups	PK Set 1_fasting_25% coating (T3) v PK Set 1_fasting _Palexia® PR 25 mg tablet (C)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.996
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9474
upper limit	1.0471

Statistical analysis title	ANOVA_PK Set 2_T1/C_AUC0-t

Statistical analysis description:

The statistical analysis of pharmacokinetic parameters was an analysis of variance (ANOVA) of the parameter AUC0-t in the Pharmacokinetic Set of Part 2 (PK set 2).
The analysis has been performed using log transformed values. The ANOVA model was fitted to the data with AUC0-t as the dependent variable, and the effects due to treatment sequence group, period, treatment, and subjects nested within sequence as fixed effects.

Comparison groups	PK Set 2_fed_15% coating (T1) v PK Set 2_fed_Palexia® PR 25 mg tablet (C)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.9489
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9062
upper limit	0.9937

Statistical analysis title	ANOVA_PK Set 2_T2/C_AUC0-t

Statistical analysis description:

The statistical analysis of pharmacokinetic parameters was an analysis of variance (ANOVA) of the parameter AUC0-t in the Pharmacokinetic Set of Part 2 (PK set 2).

The analysis has been performed using log transformed values. The ANOVA model was fitted to the data with AUC0-t as the dependent variable, and the effects due to treatment sequence group, period, treatment, and subjects nested within sequence as fixed effects.

Comparison groups	PK Set 2_fed_20% coating (T2) v PK Set 2_fed_Palexia® PR 25 mg tablet (C)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.9011
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8605
upper limit	0.9436

Other pre-specified: Primary statistical analysis of pharmacokinetic parameters_AUC

End point title	Primary statistical analysis of pharmacokinetic parameters_AUC

End point description:

Pharmacokinetic analysis of AUC of tapentadol.
The Pharmacokinetic Sets (PK Set) comprised all subjects providing sufficient data, i.e., at least Cmax or AUC0-t, to compare at least 1 of the test formulations with the reference formulation for the Pharmacokinetic Sets of Part 1 (PK Set 1) and Part 2 (PK Set 2), respectively.
Subjects were excluded from the statistical analysis of AUC if the proportion of the extrapolated area of the AUC exceeded 20%.
Therefore, the number of subject was reduced to N=22 in the subgroup "PK Set 1_fasting_20% coating versus Palexia® PR" and to N=21 in the subgroup "PK Set 1_fasting_25% coating versus Palexia® PR".

Note:
Due to the crossover design, the same subjects received different treatments within each part.
The number of subjects included in the treatment comparisons of AUC is not correct as automatically calculated by the system. The correct figure is always given in the analysis description of the different treatment comparisons.

End point type	Other pre-specified

End point timeframe:

Blood for pharmacokinetic analysis was taken up to 32 hours after IMP administration.

End point values	PK Set 1_fasting_15% coating (T1)	PK Set 1_fasting_20% coating (T2)	PK Set 1_fasting_25% coating (T3)	PK Set 2_fed_15% coating (T1)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	22[2]	21[3]	23
Units: h·ng/mL				
least squares mean (confidence interval 90%)	62.8281 (60.6197 to 65.117)	67.6169 (65.1447 to 70.1828)	73.4931 (70.7294 to 76.3648)	99.8591 (96.6037 to 103.2241)

Notes:

[2] - 1 subject was excluded from the statistical analysis of AUC as AUC%extr exceeded 20%.

[3] - 2 subjects were excluded from the statistical analysis of AUC as AUC%extr exceeded 20%.

End point values	PK Set 2_fed_20% coating (T2)	PK Set 1_fasting _Palexia® PR 25 mg tablet (C)	PK Set 2_fed_Palexia ® PR 25 mg tablet (C)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	23	23	23	
Units: h·ng/mL				
least squares mean (confidence interval 90%)	97.4753 (94.2977 to 100.7599)	70.5312 (68.0521 to 73.1007)	105.0618 (101.6369 to 108.6021)	

Statistical analyses

Statistical analysis title	ANOVA_PK Set 1_T1/C_AUC

Statistical analysis description:

The statistical analysis of pharmacokinetic parameters was an analysis of variance (ANOVA) of the parameter AUC in the Pharmacokinetic Set of Part 1 (PK Set 1). The analysis has been performed using log transformed values. The ANOVA model was fitted to the data with AUC as the dependent variable, and the effects due to treatment sequence group, period, treatment, and subjects nested within sequence as fixed effects.

Note: 23 subjects were included in this treatment comparison.

Comparison groups	PK Set 1_fasting_15% coating (T1) v PK Set 1_fasting _Palexia® PR 25 mg tablet (C)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.8908
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8469
upper limit	0.937

Statistical analysis title	ANOVA_PK Set 1_T2/C_AUC

Statistical analysis description:

The statistical analysis of pharmacokinetic parameters was an analysis of variance (ANOVA) of the parameter AUC in the Pharmacokinetic Set of Part 1 (PK Set 1). The analysis has been performed using log transformed values. The ANOVA model was fitted to the data with AUC as the dependent variable, and the effects due to treatment sequence group, period, treatment, and subjects nested within sequence as fixed effects.

Note: 22 subjects were included in this treatment comparison.

Comparison groups	PK Set 1_fasting_20% coating (T2) v PK Set 1_fasting _Palexia® PR 25 mg tablet (C)

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.9587
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9105
upper limit	1.0094

Statistical analysis title	ANOVA_PK Set 1_T3/C_AUC

Statistical analysis description:

The statistical analysis of pharmacokinetic parameters was an analysis of variance (ANOVA) of the parameter AUC in the Pharmacokinetic Set of Part 1 (PK Set 1). The analysis has been performed using log transformed values. The ANOVA model was fitted to the data with AUC as the dependent variable, and the effects due to treatment sequence group, period, treatment, and subjects nested within sequence as fixed effects.

Note: 21 subjects were included in this treatment comparison.

Comparison groups	PK Set 1_fasting_25% coating (T3) v PK Set 1_fasting _Palexia® PR 25 mg tablet (C)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.042
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9888
upper limit	1.098

Statistical analysis title	ANOVA_PK Set 2_T1/C_AUC

Statistical analysis description:

The statistical analysis of pharmacokinetic parameters was an analysis of variance (ANOVA) of the parameter AUC in the Pharmacokinetic Set of Part 2 (PK Set 2). The analysis has been performed using log transformed values. The ANOVA model was fitted to the data with AUC as the dependent variable, and the effects due to treatment sequence group, period, treatment, and subjects nested within sequence as fixed effects.

Note: 23 subjects were included in this treatment comparison.

Comparison groups	PK Set 2_fed_15% coating (T1) v PK Set 2_fed_Palexia® PR 25 mg tablet (C)

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.9505
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.907
upper limit	0.996

Statistical analysis title	ANOVA_PK Set 2_T2/C_AUC

Statistical analysis description:

The statistical analysis of pharmacokinetic parameters was an analysis of variance (ANOVA) of the parameter AUC in the Pharmacokinetic Set of Part 2 (PK Set 2). The analysis has been performed using log transformed values. The ANOVA model was fitted to the data with AUC as the dependent variable, and the effects due to treatment sequence group, period, treatment, and subjects nested within sequence as fixed effects.

Note: 23 subjects were included in this treatment comparison.

Comparison groups	PK Set 2_fed_20% coating (T2) v PK Set 2_fed_Palexia® PR 25 mg tablet (C)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.9278
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8854
upper limit	0.9722

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse event starting at the time of the first intake of tapentadol formulation until the time of the subject-related end of trial, including the washout between periods.

Adverse event reporting additional description:

The absolute and relative frequencies of subjects with any TEAEs were determined within each treatment. If an adverse event lasted longer than 1 treatment period (including washout) then it was assigned to the treatment of the period in which it first occurred.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Part 1_in fasted condition_overall

Reporting group description:

Part 1 had a 4-treatment, 4-period crossover single dose design to assess the relative bioavailability of 3 prototype tapentadol PR granule formulations (test formulations) compared to 1 tablet of Palexia® PR 25 mg (reference formulation) under fasted condition.
This arm includes all subjects allocated to treatment sequences in Part 1 with at least 1 IMP administration.

Reporting group title	Part 2_in fed condition_overall

Reporting group description:

Part 2 had a 3-treatment, 3-period crossover single dose design to assess the relative bioavailability of 2 prototype tapentadol PR granule formulations (test formulations) compared to 1 tablet of Palexia® PR 25 mg (reference formulation) under fed condition.
This arm includes all subjects allocated to treatment sequences in Part 2 with at least 1 IMP administration.

Reporting group title	Part 1_fasting_15% coating (T1)

Reporting group description:

All subjects which received a single dose of tapentadol PR 25 mg granules with coating 15% under fasted condition

Reporting group title	Part 1_fasting_20% coating (T2)

Reporting group description:

All subjects which received a single dose of tapentadol PR 25 mg granules with coating 20% under fasted condition

Reporting group title	Part 1_fasting_25% coating (T3)

Reporting group description:

All subjects which received a single dose of tapentadol PR 25 mg granules with coating 25% under fasted condition

Reporting group title	Part 1_fasting _Palexia® PR 25 mg tablet (C)

Reporting group description:

All subjects which received a single dose of Palexia® PR 25 mg tablet under fasted condition

Reporting group title	Part 2_fed_15% coating (T1)

Reporting group description:

All subjects which received a single dose of tapentadol PR 25 mg granules with coating 15% under fed condition

Reporting group title	Part 2_fed_20% coating (T2)

Reporting group description:

All subjects which received a single dose of tapentadol PR 25 mg granules with coating 20% under fed condition

Reporting group title	Part 2_fed_Palexia® PR 25 mg tablet (C)

Reporting group description:

All subjects which received a single dose of Palexia® PR 25 mg tablet under fed condition

Serious adverse events	Part 1_in fasted condition_overall	Part 2_in fed condition_overall	Part 1_fasting_15% coating (T1)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	0 / 23 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Part 1_fasting_20% coating (T2)	Part 1_fasting_25% coating (T3)	Part 1_fasting _Palexia® PR 25 mg tablet (C)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 23 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Part 2_fed_15% coating (T1)	Part 2_fed_20% coating (T2)	Part 2_fed_Palexia® PR 25 mg tablet (C)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 23 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Part 1_in fasted condition_overall	Part 2_in fed condition_overall	Part 1_fasting_15% coating (T1)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 24 (41.67%)	6 / 24 (25.00%)	4 / 23 (17.39%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	2 / 24 (8.33%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Headache			
subjects affected / exposed	5 / 24 (20.83%)	0 / 24 (0.00%)	2 / 23 (8.70%)
occurrences (all)	6	0	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 24 (12.50%)	2 / 24 (8.33%)	0 / 23 (0.00%)
occurrences (all)	3	3	0
Feeling hot			
subjects affected / exposed	1 / 24 (4.17%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 24 (8.33%)	1 / 24 (4.17%)	2 / 23 (8.70%)
occurrences (all)	2	1	2
Oral herpes			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Part 1_fasting_20% coating (T2)	Part 1_fasting_25% coating (T3)	Part 1_fasting _Palexia® PR 25 mg tablet (C)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 24 (20.83%)	0 / 23 (0.00%)	4 / 23 (17.39%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Blood creatine phosphokinase			

increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 24 (8.33%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Headache			
subjects affected / exposed	2 / 24 (8.33%)	0 / 23 (0.00%)	1 / 23 (4.35%)
occurrences (all)	2	0	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	2 / 23 (8.70%)
occurrences (all)	1	0	2
Feeling hot			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 2_fed_15% coating (T1)	Part 2_fed_20% coating (T2)	Part 2_fed_Palexia® PR 25 mg tablet (C)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 24 (16.67%)	2 / 23 (8.70%)	1 / 23 (4.35%)
Investigations			

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 24 (8.33%)	1 / 23 (4.35%)	0 / 23 (0.00%)
occurrences (all)	2	1	0
Feeling hot			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Oral herpes			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported