



## Clinical trial results:

**Perioperative administration of Tapentadol – tolerance, safety and effects on postoperative rehabilitation and quality of life.**

**Randomized, controlled study to compare the analgesic therapy with tapentadol compared to pure opioid receptor agonists**

### Summary

EudraCT number	2012-004585-18
Trial protocol	DE
Global end of trial date	21 December 2016

### Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022
Summary attachment (see zip file)	PATENT_E3 synopsis (PATENT_E3-Synopse_V02F_2017-10-24.pdf)

### Trial information

#### Trial identification

Sponsor protocol code	KKS-190
-----------------------	---------

#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	German Clinical Trials Register: DRKS00005432

Notes:

### Sponsors

Sponsor organisation name	Philipps-Universität Marburg
Sponsor organisation address	Biegenstr. 10, Marburg, Germany, 35037
Public contact	Koordinierungszentrum für Klinische Studien (KKS) Marburg, Philipps-Universität Marburg, 0049 642128 66509, info@kks.uni-marburg.de
Scientific contact	Koordinierungszentrum für Klinische Studien (KKS) Marburg, Philipps-Universität Marburg, 0049 642128 66509, info@kks.uni-marburg.de

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2016
Global end of trial reached?	Yes
Global end of trial date	21 December 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Simplified PONV Impact Scale Score [Wengritzky 2012]

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 August 2013
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: 120
Worldwide total number of subjects	120
EEA total number of subjects	120

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)	110
From 65 to 84 years	10
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

1. Medical anamnesis 2. Documentation of the premedication 3. Vital signs 4. Risk score for the occurrence of nausea and vomiting in the postoperative phase (apple score) 5. Assessment of health-related quality of life (SF-12 questionnaire).

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Tapentadol Palexia
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tapentadol Palexia @
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Other use

Dosage and administration details:

Prior surgery: routine anxiolytic (midazolam) + Tapentadol Palexia@ retard 200 mg + 90 mg Etoricoxib.

After surgery: 60 mg Etoricoxib + Tapentadol Palexia. Postoperatively, the investigational drug Palexia@ 50 mg film-coated tablets (unretarded tapentadol:) can also be taken every 30 minutes for moderate or severe pain (NRS score  $\geq 4$ ) as an analgesic indication of need. After a 12-hour observation interval, the next basic medication with Palexia® retard is administered using an adaptive dosing algorithm depending on the tapentadol dose/opioid dose requested in the previous dosing interval (analgesic medication on demand + rescue medication).

<b>Arm title</b>	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Standard Therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prior surgery: routine anxiolytic (midazolam) + 90 mg Etoricoxib.

After surgery: 60 mg Etoricoxib.

<b>Number of subjects in period 1</b>	Tapentadol Palexia	Placebo
Started	60	60
Completed	56	59
Not completed	4	1
Consent withdrawn by subject	2	1
Did not undergo surgery	1	-
received peridural anesthesia	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Tapentadol Palexia
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Tapentadol Palexia	Placebo	Total
Number of subjects	60	60	120
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	50	48	
full range (min-max)	27 to 78	35 to 76	-
Gender categorical Units: Subjects			
Female	60	60	120
Male	0	0	0

## End points

### End points reporting groups

Reporting group title	Tapentadol Palexia
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

### Primary: Simplified PONV Impact Scale Score [Wengritzky 2012]

End point title	Simplified PONV Impact Scale Score [Wengritzky 2012]
End point description:	
End point type	Primary
End point timeframe:	
24 hour postoperative	

End point values	Tapentadol Palexia	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	59		
Units: Score				
arithmetic mean (standard deviation)	15.9 ( $\pm$ 28.7)	9.7 ( $\pm$ 26.6)		

### Statistical analyses

Statistical analysis title	AUC
Statistical analysis description:	
AUC for cumulative simplified PONV Impact scale score over 48 hours postoperative.	
Comparison groups	Tapentadol Palexia v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0975
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Time between the date of informed consent and 30 days after the last administration of study medication

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	19.0
--------------------	------

### Reporting groups

Reporting group title	Tapentadol Palexia
-----------------------	--------------------

Reporting group description: -

Reporting group title	Placebo
-----------------------	---------

Reporting group description: -

Serious adverse events	Tapentadol Palexia	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 56 (1.79%)	0 / 59 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 59 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tapentadol Palexia	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 56 (92.86%)	46 / 59 (77.97%)	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	2 / 56 (3.57%)	7 / 59 (11.86%)	
occurrences (all)	2	7	
Hypotension			
subjects affected / exposed	1 / 56 (1.79%)	2 / 59 (3.39%)	
occurrences (all)	1	2	



Circulatory collapse subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	1 / 59 (1.69%) 1	
Hot flush subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 59 (0.00%) 0	
Hypertension subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 59 (0.00%) 0	
General disorders and administration site conditions			
Pain subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4	3 / 59 (5.08%) 3	
Oedema peripheral subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	3 / 59 (5.08%) 3	
Chest pain subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 59 (0.00%) 0	
Chills subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 59 (1.69%) 1	
Immune system disorders			
Hypersensitivity subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 59 (1.69%) 1	
Reproductive system and breast disorders			
Vaginal haematoma subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 59 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia subjects affected / exposed occurrences (all)	11 / 56 (19.64%) 11	3 / 59 (5.08%) 3	
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	1 / 59 (1.69%) 1	
Dyspnoea subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	2 / 59 (3.39%) 2	
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	1 / 59 (1.69%) 1	
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all)	6 / 56 (10.71%) 6	6 / 59 (10.17%) 6	
depressive s subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 59 (1.69%) 0	
Disorientation subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 59 (0.00%) 0	
Restlessness subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 59 (0.00%) 0	
Investigations C-reactive protein increased subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	1 / 59 (1.69%) 1	
Prothrombin time prolonged subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	1 / 59 (1.69%) 1	
Blood urine present subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 59 (0.00%) 0	
Injury, poisoning and procedural complications Procedural hypotension subjects affected / exposed occurrences (all)	21 / 56 (37.50%) 21	21 / 59 (35.59%) 21	
Procedural vomiting			

subjects affected / exposed	8 / 56 (14.29%)	6 / 59 (10.17%)	
occurrences (all)	8	6	
Procedural nausea			
subjects affected / exposed	6 / 56 (10.71%)	2 / 59 (3.39%)	
occurrences (all)	2	2	
Procedural pain			
subjects affected / exposed	2 / 56 (3.57%)	4 / 59 (6.78%)	
occurrences (all)	2	4	
Post procedural haemorrhage			
subjects affected / exposed	0 / 56 (0.00%)	4 / 59 (6.78%)	
occurrences (all)	0	4	
Procedural complication			
subjects affected / exposed	1 / 56 (1.79%)	1 / 59 (1.69%)	
occurrences (all)	1	1	
Procedural hypertension			
subjects affected / exposed	1 / 56 (1.79%)	1 / 59 (1.69%)	
occurrences (all)	1	1	
Post procedural complication			
subjects affected / exposed	0 / 56 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Wound haematoma			
subjects affected / exposed	0 / 56 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Wound haemorrhage			
subjects affected / exposed	0 / 56 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Wound secretion			
subjects affected / exposed	0 / 56 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 56 (3.57%)	1 / 59 (1.69%)	
occurrences (all)	2	1	
Bradycardia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 59 (0.00%)	
occurrences (all)	1	0	

Extrasystoles subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 59 (1.69%) 1	
Sinus tachycardia subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 59 (1.69%) 1	
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	3 / 59 (5.08%) 3	
Dizziness subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	0 / 59 (0.00%) 0	
sensory subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 59 (0.00%) 0	
Tremor subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 59 (0.00%) 0	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	3 / 59 (5.08%) 3	
Leukocytosis subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2	0 / 59 (0.00%) 0	
Haemorrhagic anaemia subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 59 (0.00%) 0	
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 59 (0.00%) 0	
Gastrointestinal disorders			
Flatulence subjects affected / exposed occurrences (all)	9 / 56 (16.07%) 9	10 / 59 (16.95%) 10	

Constipation subjects affected / exposed occurrences (all)	10 / 56 (17.86%) 10	6 / 59 (10.17%) 6	
Nausea subjects affected / exposed occurrences (all)	7 / 56 (12.50%) 7	1 / 59 (1.69%) 1	
Vomiting subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2	1 / 59 (1.69%) 1	
Abdominal pain subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 59 (1.69%) 1	
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 59 (1.69%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 59 (0.00%) 0	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2	1 / 59 (1.69%) 1	
Rash subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 59 (0.00%) 0	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2	4 / 59 (6.78%) 4	
Musculoskeletal pain subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	1 / 59 (1.69%) 1	
Infections and infestations Blood glucose abnormal subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 59 (1.69%) 1	

Urinary tract infection subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2	0 / 59 (0.00%) 0	
Nosocomial infection subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 59 (1.69%) 1	
Pneumonia subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 59 (0.00%) 0	
Metabolism and nutrition disorders			
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	3 / 59 (5.08%) 3	
Acidosis subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	1 / 59 (1.69%) 1	
Hypocalcaemia subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 1	0 / 59 (0.00%) 0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 July 2015	Indication: Reduction to one indication (hysterectomy), thus stratification at randomization was also omitted. The planned number of patients was reduced from 150 to 120. The ECG before surgery was omitted due to complex surgical hygiene.

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported