Clinical trial results:
Efficacy and Safety of Prolonged Release (SR) Tramadol Hydrochloride (HCl)/Paracetamol fixed combination and Immediate Release (IR) Tramadol HCl/Paracetamol fixed combination in Patients with Moderate to Severe Acute Low-Back Pain - TreaSuRe

Summary

EudraCT number	2015-002875-20
Trial protocol	SI CZ HR PL
Global end of trial date	18 December 2017

Results information

Result version number	v1
This version publication date	31 May 2020
First version publication date	31 May 2020
Summary attachment (see zip file)	Treasure_Final_Report_Synopsis (Final_report_SYNOPSIS_KCT03-2015_TREASURE-15052020.pdf)

Trial information

Trial identification

Sponsor protocol code	KCT03/2015–DORETA

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Krka d.d., Novo mesto
Sponsor organisation address	Dunajska cesta 65, Ljubljana, Slovenia, 1000
Public contact	Tanja Kohek, Krka d.d., Novo mesto Dunajska cesta 65 1000 Ljubljana Slovenia, 00386 41 589769, tanja.kohek@krka.biz
Scientific contact	Tanja Kohek, Krka d.d., Novo mesto Dunajska cesta 65 1000 Ljubljana Slovenia, 00386 41 589769, tanja.kohek@krka.biz
Sponsor organisation name	Krka ČR s.r.o.
Sponsor organisation address	Sokolovská 192/79, Prague, Czech Republic, 180 00
Public contact	Martin Sustr, Krka ČR s.r.o. Sokolovská 192/79 180 00 Prague Czech Republic, 00420 602 486846, martin.sustr@krka.biz
Scientific contact	Martin Sustr, Krka ČR s.r.o. Sokolovská 192/79 180 00 Prague Czech Republic, 00420 602 486846, martin.sustr@krka.biz

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	24 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 December 2017
Global end of trial reached?	Yes
Global end of trial date	18 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main objective of the trial is to evaluate the efficacy, safety and effects on Quality of Life (QOL) of the medicines Doreta IR and Doreta SR produced by Krka, d.d., Novo mesto, Slovenia in patients with moderate to severe acute low-back pain.

Protection of trial subjects:

Pain assessment was made at the control visits at day 7, 14 and 28 after therapy initiation to obtain data for the primary and secondary efficacy endpoints analysis. Principal methodology was the back pain intensity assessment by means of Visual analogue scale (VAS), Brief pain inventory short form and Quality Of Life (QOL) questionnaire.

Background therapy:

Patients were given naproxen sodium 550 mg (Nalgesin® forte) and are instructed to take two tablet daily in addition to IMP as a rescue therapy, but only if they consider that pain intensity is too high (despite taking Doreta®) over the last 8 hours.
Patients were also given pantoprazole 20 mg (Nolpaza®) and are instructed to take one tablet in the morning 1 hour before a meal with some water to prevent peptic ulcers that can occur as a side effect of non-steroidal anti-inflammatory drugs (NSAIDs), such as naproxen sodium.

Evidence for comparator: -

Actual start date of recruitment	19 September 2016
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	Poland: 70
Country: Number of subjects enrolled	Slovenia: 40

Country: Number of subjects enrolled	Croatia: 103
Country: Number of subjects enrolled	Czech Republic: 100
Worldwide total number of subjects	313
EEA total number of subjects	313

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)	248
From 65 to 84 years	65
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

316 patients screened from Croatia, Czech Republic, Poland and Slovenia. First patient in on 19.9.2016, last patient concluded on 18.12.2017. At first it was planned that the study will be performed also in Romania (70 patients). Because of the nonresponsiveness of Romanian Agency for Medicines (NAMMDR) the study conduct in Romania was cancelled.

Pre-assignment

Screening details:

In general, eligible patients for the screening procedure for the enrolment were adult patients aged 18-75 years, of both genders, with previously treated or untreated low back pain of moderate to severe intensity (according to the VAS threshold value), who currently do not participate in another clinical trial.

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	Instant Release Tramadol/Paracetamol FDC

Arm description:

Patients in Instant Release Tramadol/Paracetamol FDC arm were taking four tablets of IR-TPFC 37,5 mg/325 mg per day, one every 6 hours.

Arm type	Experimental
Investigational medicinal product name	Doreta®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet 37,5 mg/325 mg every 6 hours

Arm title	Sustained Release Tramadol/Paracetamol FDC

Arm description:

Patients in Sustained Release Tramadol/Paracetamol FDC arm were taking two tablets SR-TPFC 75 mg/650 mg per day, one every 12 hours.

Arm type	Experimental
Investigational medicinal product name	Doreta® SR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

One SR-TPFC tablet 75 mg/650 mg every 12 hours.

Number of subjects in period 1	Instant Release Tramadol/Paracetamol FDC	Sustained Release Tramadol/Paracetamol FDC
Started	157	156
Completed	148	145
Not completed	9	11
Consent withdrawn by subject	4	1
Adverse event, non-fatal	2	5
Lost to follow-up	-	1
Protocol deviation	3	4

Baseline characteristics

Reporting groups	
Reporting group title	Instant Release Tramadol/Paracetamol FDC
Reporting group description:	
Patients in Instant Release Tramadol/Paracetamol FDC arm were taking four tablets of IR-TPFC 37,5 mg/325 mg per day, one every 6 hours.	
Reporting group title	Sustained Release Tramadol/Paracetamol FDC
Reporting group description:	
Patients in Sustained Release Tramadol/Paracetamol FDC arm were taking two tablets SR-TPFC 75 mg/650 mg per day, one every 12 hours.	

Reporting group values	Instant Release Tramadol/Paracetamol FDC	Sustained Release Tramadol/Paracetamol FDC	Total
Number of subjects	157	156	313
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			
arithmetic mean	50.2	51.5	
standard deviation	± 13.6	± 13.9	-
Gender categorical			
In PP analysis set data about gender are as following: 106 male, 158 female and 1 patient without data about gender.			
Units: Subjects			
Female	94	96	190
Male	63	60	123

Subject analysis sets	
Subject analysis set title	ITT - Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Eligible patients that were enrolled in the study, but had small deviations from the study protocol.	
Subject analysis set title	PP - Per protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
Eligible patients that were enrolled in the study and completed the study according to the protocol.	

Reporting group values	ITT - Intention to treat	PP - Per protocol	
Number of subjects	313	265	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	50.9	NA	
standard deviation	± 13.8	±	
Gender categorical			
In PP analysis set data about gender are as following: 106 male, 158 female and 1 patient without data about gender.			
Units: Subjects			
Female	190		
Male	123		

End points

End points reporting groups

Reporting group title	Instant Release Tramadol/Paracetamol FDC
Reporting group description:	
Patients in Instant Release Tramadol/Paracetamol FDC arm were taking four tablets of IR-TPFC 37,5 mg/325 mg per day, one every 6 hours.	
Reporting group title	Sustained Release Tramadol/Paracetamol FDC
Reporting group description:	
Patients in Sustained Release Tramadol/Paracetamol FDC arm were taking two tablets SR-TPFC 75 mg/650 mg per day, one every 12 hours.	
Subject analysis set title	ITT - Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Eligible patients that were enrolled in the study, but had small deviations from the study protocol.	
Subject analysis set title	PP - Per protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
Eligible patients that were enrolled in the study and completed the study according to the protocol.	

Primary: The proportion of patients with clinically meaningful improvement of low back pain at the regular therapy end visit, i.e. Visit 2, Visit 3 or Visit 4.

End point title	The proportion of patients with clinically meaningful improvement of low back pain at the regular therapy end visit, i.e. Visit 2, Visit 3 or Visit 4.
End point description:	
Statistical methods were used to compare bot arms - Immediate Relase and Sustained Release Tramadol/Paracetamol FDC.	
End point type	Primary
End point timeframe:	
For one patient from 1 to 4 weeks for whole study (19.9.2016 to 18.12.2017). Investigators had an option to conclude the treatment earlier than 4 weeks after the initiation in case patient has reached the target reduction of pain (less tha 30 mm on VAS).	

End point values	Instant Release Tramadol/Paracetamol FDC	Sustained Release Tramadol/Paracetamol FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	156		
Units: mm on VAS scale				
arithmetic mean (standard deviation)				
Pain intensity in mm on VAS at Baseline	70.3 (± 13.0)	72.0 (± 12.8)		
Pain intensity in mm on VAS on Visit 2	40.7 (± 22.5)	40.1 (± 23.2)		
Pain intensity in mm on VAS on Visit 3	35.4 (± 20.5)	34.2 (± 20.4)		
Pain intensity in mm on VAS on Visit 4	16.3 (± 19.6)	14.6 (± 18.2)		

Statistical analyses

Statistical analysis title	Non-inferiority test of the primary endpoint

Statistical analysis description:

We have performed the non-inferiority test associated to the primary endpoint by employing the one-sided asymptotic 95%-confidence interval for the difference pSR-pIR obtained by multiple imputation. The inferiority hypothesis of Group SR-TPFC in relation with Group IR-TPFC is to be rejected if the computed confidence interval for pSR-pIR lies strictly above -0.2.

Comparison groups	Instant Release Tramadol/Paracetamol FDC v Sustained Release Tramadol/Paracetamol FDC
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	Wang exact 95%-confidence interval
Parameter estimate	difference between p(SR)-p(IR)
Point estimate	0.044
Confidence interval	
level	95 %
sides	1-sided
lower limit	-0.028

Notes:

[1] - We have performed the non-inferiority test by employing the one-sided exact 95%-confidence interval for the difference pSR-pIR due to Wang (The Annals of Statistics, 2010) and as implemented by Shan and Wang.

Secondary: Pain intensity difference (PID) between pain intensity on baseline and on day 6

End point title	Pain intensity difference (PID) between pain intensity on baseline and on day 6

End point description:

Test of equality of expected differnces was used to compare bot arms - Immediate Relase and Sustained Release Tramadol/Paracetamol FDC.

End point type	Secondary

End point timeframe:

6 days - PID was evaluated on day 6 of the treatment.

End point values	Instant Release Tramadol/Paracetamol FDC	Sustained Release Tramadol/Paracetamol FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	156		
Units: mm on VAS				
arithmetic mean (standard deviation)				
Pain in mm on VAS at Baseline	70.3 (± 13.0)	72.0 (± 12.8)		
Pain in mm on VAS on day 6	43.0 (± 22.1)	42.5 (± 20.5)		
Difference	-27.3 (± 25.7)	-29.5 (± 21.9)		

Statistical analyses

Statistical analysis title	PID difference between IR arm and SR arm
Comparison groups	Instant Release Tramadol/Paracetamol FDC v Sustained

	Release Tramadol/Paracetamol FDC
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Parameter estimate	Mean difference (final values)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.13
upper limit	7.5

Notes:

[2] - Negative difference between measurement at baseline and beginning of the day 6 means improvement (less pain). PID for IR-TPFC was -27.3 and for SR-TPFC was -29.5. Difference between the groups was 2.2 mm on VAS scale in favor of SR-TPFC (95% CI -3.13, 7.5]. The test of equality of expected differences in Group SR-TPFC and Group IR-TPFC yields a statistically non-significant difference between the two groups.

Secondary: Cumulative pain intensity (CPI) endpoints

End point title	Cumulative pain intensity (CPI) endpoints

End point description:

End point type	Secondary

End point timeframe:

15 days - Cumulative pain intensity (CPI) was assessed on day 2, 3, 6, 8 and 15. There were 5 assessments during the day - Right before the first IMP dose of the day and 2, 6, 8 and 12 hours after the first dose of IMP of the day.

End point values	Instant Release Tramadol/Paracetamol FDC	Sustained Release Tramadol/Paracetamol FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	156		
Units: mm on VAS				
arithmetic mean (standard deviation)				
CPI day 2	271.2 (± 86.2)	277.6 (± 89.6)		
CPI day 3	235.1 (± 87.6)	238.3 (± 92.5)		
CPI day 6	185.8 (± 106.4)	189.5 (± 104.1)		
CPI day 8	201.5 (± 96.5)	196.3 (± 101.9)		
CPI day 15	168.0 (± 103.7)	160.5 (± 101.5)		

Statistical analyses

Statistical analysis title	Cumulative pain intensity

Statistical analysis description:

Test of equality for CPI on day 2, 3, 6, 8 and 15 yielded statistically non-significant differences between IR-TPFC group and SR-TPFC group. The largest difference 7.4 mm (95% CI -22.8; 37.6)was on day 15

with higher mean, thus higher pain intensity, in IR-TPFC group.

Comparison groups	Instant Release Tramadol/Paracetamol FDC v Sustained Release Tramadol/Paracetamol FDC
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference (final values)
Point estimate	7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.7
upper limit	37.63

Secondary: Cumulative pain intensity (CPI) difference between day 2 and day 3, day 6, day 8 and day 15

End point title	Cumulative pain intensity (CPI) difference between day 2 and day 3, day 6, day 8 and day 15

End point description:

The difference between CPI measured on day 2 with CPI measured on day 3, 6, 8, and 15 yielded statistically significant results for both therapeutic groups. The difference between CPI on day 2 and day 3 was 36.2 mm and 39.4 mm, in IR-TPFC and SR-TPFC group respectively, which yielded a statistically significant reduction of CPI already from day 2 to day 3. The differences between CPI on day 2 and all following measurements on day 6, 8 and 15 were statistically significant. The highest difference, 105.1 mm and 133.1 mm in IR-TPFC and SR-TPFC group respectively, was between measurement on day 2 and day 15.

End point type	Secondary

End point timeframe:

14 days - assessments between day 2 and day 15 of the IMP

End point values	Instant Release Tramadol/Paracetamol FDC	Sustained Release Tramadol/Paracetamol FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	156		
Units: mm on VAS				
arithmetic mean (standard deviation)				
CPI difference between day 2 and day 3	-36.2 (± 42.8)	-39.4 (± 41.6)		
CPI difference between day 2 and day 6	-85.4 (± 80.0)	-88.1 (± 77.2)		
CPI differnece between day 2 and day 8	-72.1 (± 64.0)	-89.1 (± 80.0)		
CPI difference between day 2 and day 15	-105.1 (± 94.4)	-133.1 (± 88.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pain intensity difference (PID) endpoints

End point title	Pain intensity difference (PID) endpoints

End point description:

The baseline and the final values are nominally between 0 and 100 mm; the difference is nominally between -100 and 100 mm. A higher value of pain intensity means more pain; thus, a negative difference here means improvement. The test of equality of expected differences in Group SR-TPFC and Group IR-TPFC yields a statistically non-significant difference between the two groups.

End point type	Secondary

End point timeframe:

Up to 4 weeks - PID 2 at visit 2 (1 week), PID 3 at visit 3 (2 weeks) and PID 4 at visit 4 (4 weeks).

End point values	Instant Release Tramadol/Paracetamol FDC	Sustained Release Tramadol/Paracetamol FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	156		
Units: mm on VAS				
arithmetic mean (standard deviation)				
PID 2 (1 week)	-29.7 (± 25.2)	-31.9 (± 24.2)		
PID 3 (2 weeks)	-33.3 (± 24.9)	-37.3 (± 23.2)		
PID 4 (4 weeks)	-54.1 (± 25.1)	-57.4 (± 22.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life (QOL) difference

End point title	Quality of life (QOL) difference

End point description:

Quality of life was assessed by health domains created based on the 36-Item Short Form Survey from the RAND Medical Outcomes Study (MOS). All domains were individually analysed at the Visit 1 (baseline) and Visit 4 (week 4). Each of this measurements were normalized on a scale from 0 (the state of corresponding component is worst) to 100 (the state of the corresponding component is best). The results are thus to be interpreted as: more positive is the difference in each SF-36 domain, the more has analysed aspect of QOL improved.
Differences of all domains were positive and were, except for Emotional well-being in SR-TPFC group, all statistically significant. The test of equality of expected differences in Group SR-TPFC and Group IR-TPFC yields a statistically non-significant difference between the two groups.

End point type	Secondary

End point timeframe:

4 weeks - From Visit 1 (baseline) to Visit 4 (week 4)

End point values	Instant Release Tramadol/Paracetamol FDC	Sustained Release Tramadol/Paracetamol FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	156		
Units: points				
arithmetic mean (standard deviation)				
Physical functioning	43.0 (± 33.3)	41.8 (± 34.5)		
Role functioning/physical	8.8 (± 40.3)	10.0 (± 45.0)		
Role functioning/emotional	11.7 (± 38.6)	10.7 (± 42.1)		
Energy/fatigue	6.9 (± 21.5)	5.3 (± 19.9)		
Emotional well-being	3.5 (± 20.4)	2.8 (± 20.1)		
Social functioning	9.0 (± 25.9)	7.3 (± 26.3)		
Pain	12.2 (± 27.2)	13.6 (± 31.1)		
General health	4.6 (± 15.6)	4.3 (± 17.8)		
Health change	12.6 (± 31.2)	14.4 (± 29.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Interference Score difference (dPIS) on Visit 2

End point title	Pain Interference Score difference (dPIS) on Visit 2

End point description:

The Pain Interference Score (PIS) for each category is scaled from 0 to 10, with results to be interpreted as: the lower the mean PIS, the less pain interferes with the particular activity (negative dPIS therefore means less pain on the following visit). For each of the seven categories dPIS was assessed, which denotes the difference between pain interference score at Visit 2, 3 and 4 and the baseline score at Visit 1 for each of the therapy groups.
In both therapeutic groups, IR-TPFC and SR-TPFC, there were statistically significant improvements noted for all Pain Interference Scores (7 categories) at any of the subsequent visits with respect to the baseline values. Regardless of the treatment group significant improvements were noted already at Visit 2 with respect to the baseline values for all 7 categories.
The differences between the IR-TPFC and SR-TPFC group in the PIS reduction were consistently non-significant for all 7 categories over all three visits.

End point type	Secondary

End point timeframe:

1 week - From Visit 1 (baseline) to Visit 2 (week 1)

End point values	Instant Release Tramadol/Paracetamol FDC	Sustained Release Tramadol/Paracetamol FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	156		
Units: points				
arithmetic mean (standard deviation)				
General Activity dPIS	-1.90 (± 2.20)	-1.96 (± 2.20)		
Mood dPIS	-1.84 (± 2.47)	-1.92 (± 2.29)		
Walking Ability dPIS	-1.35 (± 2.37)	-1.82 (± 2.33)		

Normal Work dPIS	-1.75 (± 2.39)	-2.10 (± 2.30)		
Relation with other people dPIS	-1.09 (± 2.47)	-1.59 (± 2.39)		
Sleep dPIS	-2.18 (± 2.40)	-2.24 (± 2.58)		
Enjoyment of Life dPIS	-1.71 (± 2.61)	-2.04 (± 2.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Interference Score difference (dPIS) on Visit 3

End point title	Pain Interference Score difference (dPIS) on Visit 3

End point description:

The Pain Interference Score (PIS) for each category is scaled from 0 to 10, with results to be interpreted as: the lower the mean PIS, the less pain interferes with the particular activity (negative dPIS therefore means less pain on the following visit). For each of the seven categories dPIS was assessed, which denotes the difference between pain interference score at Visit 2, 3 and 4 and the baseline score at Visit 1 for each of the therapy groups.
In both therapeutic groups, IR-TPFC and SR-TPFC, there were statistically significant improvements noted for all Pain Interference Scores (7 categories) at any of the subsequent visits with respect to the baseline values. Regardless of the treatment group significant improvements were noted already at Visit 2 with respect to the baseline values for all 7 categories.
The differences between the IR-TPFC and SR-TPFC group in the PIS reduction were consistently non-significant for all 7 categories over all three visits.

End point type	Secondary

End point timeframe:

2 weeks - From Visit 1 (baseline) to Visit 3 (week 2)

End point values	Instant Release Tramadol/Paracetamol FDC	Sustained Release Tramadol/Paracetamol FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	156		
Units: points				
arithmetic mean (standard deviation)				
General Activity dPIS	-2.94 (± 2.43)	-3.13 (± 2.45)		
Mood dPIS	-3.03 (± 2.70)	-3.28 (± 2.47)		
Walking Ability dPIS	-2.52 (± 2.50)	-2.94 (± 2.47)		
Normal Work dPIS	-2.79 (± 2.60)	-3.40 (± 2.37)		
Relation with other people dPIS	-2.21 (± 2.89)	-2.64 (± 2.63)		
Sleep dPIS	-3.35 (± 2.80)	-3.22 (± 2.87)		
Enjoyment of Life dPIS	-2.94 (± 2.87)	-3.12 (± 2.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Interference Score difference (dPIS) on Visit 4

End point title	Pain Interference Score difference (dPIS) on Visit 4

End point description:

The Pain Interference Score (PIS) for each category is scaled from 0 to 10, with results to be interpreted as: the lower the mean PIS, the less pain interferes with the particular activity (negative dPIS therefore means less pain on the following visit). For each of the seven categories dPIS was assessed, which denotes the difference between pain interference score at Visit 2, 3 and 4 and the baseline score at Visit 1 for each of the therapy groups.
In both therapeutic groups, IR-TPFC and SR-TPFC, there were statistically significant improvements noted for all Pain Interference Scores (7 categories) at any of the subsequent visits with respect to the baseline values. Regardless of the treatment group significant improvements were noted already at Visit 2 with respect to the baseline values for all 7 categories.
The differences between the IR-TPFC and SR-TPFC group in the PIS reduction were consistently non-significant for all 7 categories over all three visits.

End point type	Secondary

End point timeframe:

4 weeks - from Visit 1 (baseline) to Visit 4 (week 4)

End point values	Instant Release Tramadol/Paracetamol FDC	Sustained Release Tramadol/Paracetamol FDC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	156		
Units: points				
arithmetic mean (standard deviation)				
General Activity dPIS	-4.87 (± 2.95)	-4.95 (± 2.82)		
Mood dPIS	-4.87 (± 2.74)	-4.63 (± 2.75)		
Walking Ability dPIS	-3.96 (± 2.95)	-4.43 (± 2.96)		
Normal Work dPIS	-4.50 (± 2.92)	-4.83 (± 2.66)		
Relation with other people dPIS	-3.35 (± 2.93)	-3.81 (± 2.72)		
Sleep dPIS	-4.69 (± 2.80)	-4.60 (± 2.65)		
Enjoyment of Life dPIS	-4.34 (± 3.26)	-4.42 (± 3.01)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE reporting timeframe for one patient was up to 4 weeks and was the same for the whole duration of the study (from the day the first patient entered (19.9.2016) to the day the last patient concluded the study (18.12.2017)).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Instant Release Tramadol/Paracetamol FDC
Reporting group description: -	
Reporting group title	Sustained Release Tramadol/Paracetamol FDC

Reporting group description: -

Serious adverse events	Instant Release Tramadol/Paracetamol FDC	Sustained Release Tramadol/Paracetamol FDC	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 157 (0.00%)	0 / 156 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Instant Release Tramadol/Paracetamol FDC	Sustained Release Tramadol/Paracetamol FDC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 157 (40.76%)	63 / 156 (40.38%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	24 / 157 (15.29%)	20 / 156 (12.82%)	
occurrences (all)	27	25	
Somnolence			
subjects affected / exposed	10 / 157 (6.37%)	11 / 156 (7.05%)	
occurrences (all)	16	19	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	30 / 157 (19.11%)	28 / 156 (17.95%)	
occurrences (all)	37	35	
Constipation			
subjects affected / exposed	21 / 157 (13.38%)	21 / 156 (13.46%)	
occurrences (all)	26	35	
Vomiting			
subjects affected / exposed	10 / 157 (6.37%)	7 / 156 (4.49%)	
occurrences (all)	10	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 April 2017	The purpose of the Protocol ammendment was the addition of 5 new sites in Slovenia.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported