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

Final report synopsis

Trial Protocol No. KCT 03/2015 – TREASURE
EudraCT No. 2015-002875-20

September 2019

KRKA

1 INTEGRATED CLINICAL STUDY REPORT

1. Study title:

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

2. Names of Tested investigational medicinal products (IMPs):

Doreta® IR: Tramadol hydrochloride/Paracetamol 37.5 mg/325 mg film-coated tablets (IR-TPFC)
Doreta® SR: Tramadol hydrochloride/Paracetamol 75 mg/650 mg prolonged-release tablets (SR-TPFC)

3. Indication studied:

Acute moderate to severe back pain

4. Study design:

A randomized, open-label, parallel, active-control, two-arm, comparative, multi-center study with international character. Patients with acute back pain of various aetiologies were randomly assigned to receive tramadol/paracetamol immediate release formulation (IR-TPFC) or tramadol/paracetamol sustained release formulation (SR-TPFC). They have been treated for up to 28 days and study parameters assessed at up to four visits. Initial doses of the two investigational medicinal products (IMP) have been applied and pain assessment 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. For the purpose of efficacy and safety assessment, patients have also completed diaries on days 2, 3, 6, 8 and 15 of the therapy. Quality of life (QOL) has been assessed at the initial and final visits using questionnaires. At each visit following the initiation of therapy, drug compliance has been assessed. Investigators have had an option to conclude the treatment earlier than 28 days after the initiation in case patient has reached the target reduction of pain as a criterion of successful treatment. Notwithstanding, all the patients have been obliged to attend the visit 4 at day 28 for the final therapeutic assessment.
Patients have also had an option to take the standardised rescue treatment in case of unbearable pain while having been treated with the IMP.

5. Sponsor:

Krka d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

6. Protocol identification number:

KCT 03/2015 – TREASURE

7. Development phase of the study:

Phase IIIb/IV

8. Study initiation date (first subject enrolled):

19.9.2016

9. Study completion date (last subject completed):

18.12.2017

10. Name and affiliation of principal investigators:

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12. Statement:

This trial has been performed in compliance with the Good Clinical Practices (GCP/ ICH E6 (R2) including the archiving of essential documents.

13. Authors of the clinical study report:

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14. Date of the report:

September 2019

2 STUDY SYNOPSIS

Name of the sponsor:

Krka, tovarna zdravil, d. d., Novo mesto

Name of the finished product:

Doreta® IR: Tramadol hydrochloride/Paracetamol 37.5 mg/325 mg film-coated tablets (IR-TPFC)
Doreta® SR: Tramadol hydrochloride/Paracetamol 75 mg/650 mg prolonged-release tablets (SR-TPFC)

Name of the active ingredients:

Tramadol hydrochloride/Paracetamol

Title of Study:

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.

Investigators:

Altogether, 44 investigators participated in the study from four countries; 19 of those were from SI, 11 from PL, 11 from HR and 3 from CZ.

Country	Number of trial sites	Number of investigators
Slovenia	11	19
Poland	6	11
Croatia	5	11
Czech republic	3	3
TOTAL	25	44

The full list of investigators is provided in section 6. The list of distribution of patients per country is provided in section 14.1 and the list of institutions and number of patients enrolled is provided in the section **Napaka! Vira sklicevanja ni bilo mogoče najti.**.

Studied Period (1.3 year) Date of first patient entered: • 19-Sept-2016 Date of last patient concluded • 18-Dec-2017	**Phase of development:** Phase IIIb/IV

Objectives:

The purpose of the study is to evaluate the efficacy, safety and effects on Quality of Life (QOL) of the medicines tramadol/paracetamol immediate release fixed combination (IR-TPFC) and tramadol/paracetamol sustained release fixed combination (SR-TPFC) produced by Krka, d.d., Novo mesto, Slovenia in patients with moderate to severe acute low-back pain.

Methodology/Study Design:

Randomized, open-label, prospective, comparative, two-arm, multi-center, international clinical trial.
Patients with acute back pain of various aetiologies were randomly assigned to receive IR-TPFC or SR-TPFC. They have been treated for up to 28 days and study parameters assessed at up to four visits. Initial doses of the two investigational medicinal products (IMP) have been applied and pain assessment 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. For the purpose of efficacy and safety assessment, patients have also completed diaries on days 2, 3, 6, 8 and 15 of the therapy. QOL has been assessed at the initial and final visits using questionnaires. At each visit following the initiation of therapy, drug compliance has been assessed.
Investigators have had an option to conclude the treatment earlier than 28 days after the initiation in case patient has reached the target reduction of pain as a criterion of successful treatment. Notwithstanding, all the patients have been obliged to attend the visit 4 at day 28 for the final therapeutic assessment.
Patients also have had an option to take the standardised rescue treatment in case of unbearable pain while having been treated with the IMP.
Principal methodology was the back pain intensity assessment by means of Visual analogue scale (VAS), Brief pain inventory short form and QOL questionnaire. Compliance was assessed by pill counting, treatment days counting and subsequent calculation according to standard drug compliance equation.
Data management was based on the electronic data capture (EDC).

Number of patients:

Planned:
- Randomised: 350
- Finished per protocol: 250

Analysed:
- Screened/randomized patients: 316
- Analysed for efficacy and safety endpoints (ITT analysis): 313
- Analysed for efficacy endpoints (PP analysis): 265

Diagnosis and main criteria for inclusion:

Patients with acute moderate to severe back pain.

Main inclusion criteria:

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.

IMPs:

- Doreta® IR: Tramadol hydrochloride/Paracetamol 37.5 mg/325 mg film-coated tablets (IR-TPFC)
- Doreta® SR: Tramadol hydrochloride/Paracetamol 75 mg/650 mg prolonged-release tablets (SR-TPFC)

Dose and mode of administration:

- IR-TPFC: Four tablets daily (one tablet each 6 hours)
- SR-TPFC: Two tablets daily (one tablet each 12 hours)

Batch numbers:

- IR-TPFC: D52180, D51830, D51725, D52267
- SR-TPFC: SA3774, SA3812, SB0622

Duration of treatment :

The duration of treatment was 28 days.

Efficacy criteria for evaluation:

Primary efficacy endpoint:

- 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. It is the decision of the investigator to conclude the successful treatment earlier (Visit 2 or Visit 3). Reduction of low back pain intensity is considered as clinically meaningful if pain intensity measurement does not exceed 30 mm on VAS.

Secondary efficacy endpoints:

- Pain intensity difference (PID) at the beginning of dosing interval on day 6 (one endpoint).
- Cumulative pain intensity (CPI) throughout the dosing interval (five endpoints).
- Pain intensity difference between each control visit value and the baseline value at Visit 1 (three endpoints).
- Quality of life difference (nine endpoints).
- Pain interference score difference (assessed by Brief pain inventory - Short form) between the value at each visit and the baseline value at Visit 1 (twenty one endpoints).
- Proportion of patients with excellent pain response (one endpoint).
- Proportion of patients with reduced pain at each control visit (three endpoints).
- Proportion of patients with eliminated pain: at each control visit (three endpoints).
- Proportion of compliant patients, i.e. those having a compliance of more than 80% at the regular therapy end visit (one endpoint).

Safety criteria for evaluation:

- Short-term tolerability of IR-TPFC and SR-TPFC, evaluated by patients, using a diary to monitor four common adverse reactions (nausea, dizziness, vomiting, constipation at days 2, 3, 6, 8 and 15).
- Overall incidence of adverse reactions (drug-related adverse events).
- Incidence of adverse reactions stratified by specific type of adverse reaction.
- A number/percentage of patients unable to finish treatment periods due to clinically significant adverse reaction.

Statistical methods:
The methods associated with the per-protocol (PP) set, the methods used to compare the two treatment groups at baseline, and the methods associated with the safety set were implemented on observed data. To be able to demonstrate non-inferiority of one treatment group to another on the PP set, a set of 250 per-protocol patients in both groups was deemed adequate; for the primary efficacy endpoint analysis we employed the Wang exact confidence interval for the difference of two proportions, assuming a non-inferiority margin of 0.2 and significance level of 0.05. To assess proportions connected with the primary endpoint on the PP set, we used the Clopper-Pearson exact confidence interval. For comparison of the treatment groups at baseline, we used the unpaired t-test (for ratio-scale variables), Wang's confidence interval for the difference of two proportions, the chi-square test (for categorical variables), and the unpaired asymptotic z-test (for discrete variables). Detailed descriptive statistics were computed for the evaluation of adverse events. For comparative analyses associated with adverse events, we used the Wang exact confidence interval for the difference of two proportions, and the Wilcoxon-Mann-Whitney test (for rank variables).
To deal with missing values, multiple imputation methods were used for all inference on the ITT set; five completed datasets were created by Bayesian multiple imputations and the inference based on them was made by pooling in the sense of Rubin.
The level of significance for tests of hypotheses was 0.05, corresponding to the confidence level of 95% for confidence interval. No corrections for multiple comparisons have been made.

All statistical methods are described in details in Statistical analysis plan.

Summary of results and conclusions:

EFFICACY RESULTS

Baseline characteristics

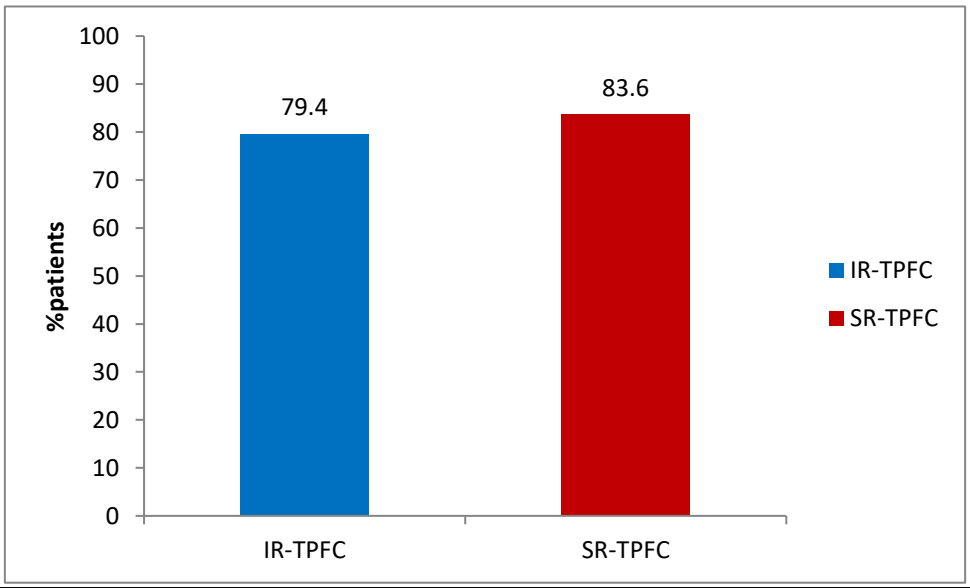
Average duration of low back pain was around 14.1 days in both therapeutic groups. In the last 12 months 96 patients in therapy group IR-TPFC (30.7%) and 77 patients in therapy group SR-TPFC (24.6%) had previous treatment of low back pain; in majority of patients the pain was managed with NSAID and opioid medicines. At baseline, there were no differences between the two populations with respect to relevant parameters of demographics, vital signs, previous and current comorbid conditions and previous intake of any drugs in the last 30 days. The single statistically significant difference in the previous treatment of low back pain between the groups is not deemed clinically significant.
The mean values of baseline pain score were approximately at the upper level of moderate pain i.e. 70.3mm (range 40-100 mm) in the IR-TPFC group, and 71.9 mm in SR-TPFC group (range 40-100 mm). The baseline assessment of back pain with VAS revealed no significant difference between the treatment groups. Analysis of other baseline characteristics revealed no significant difference between the two groups. There were altogether 20 premature exclusions mostly due to adverse events and protocol violations. The most common protocol violation type was inadequate study treatment duration. Patient compliance was more than 90% with no evident difference between the two groups.

Primary efficacy endpoint

- Clinically meaningful improvement (CMI %)

As primary efficacy endpoint was evaluated the percentage of patients reaching target reduction of pain intensity (VAS ≤ 30mm). In the per protocol population setting, altogether 79.4% in IR-TPFC group and 83.6% in SR-TPFC group have reached therapeutic goal with the 95% CI entirely within the non-inferiority margin of 20% (Figure 1). The hypothesis of inferiority of SR-TPFC with respect to IR-TPFC was therefore rejected and hence the former is considered non-inferior with respect to the latter. The difference between the two groups was 4% in favour of SR-TPFC, which is deemed not to be statistically significant. The ITT analysis showed the same picture with 84.0% and 79.6% patient reaching the target reduction of pain intensity in SR-TPFC and IR-TPFC, respectively and 95% CI within the margin of non-inferiority.

Figure 1: Percentage of patients reaching the target pain intensity reduction, PP population



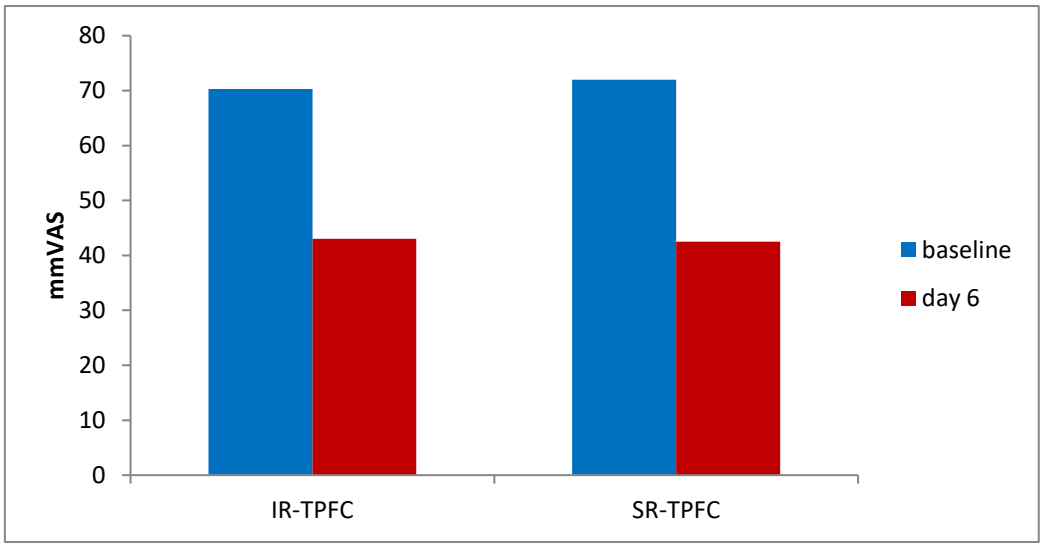
Secondary efficacy endpoints

By and large, all secondary efficacy endpoints yielded statistically non-significant differences between the two groups. Both therapeutic groups provided high efficacy during the treatment. Significant improvement of the studied drugs in reducing the low back pain, pain interference with daily activities and quality of life was achieved during the treatment with respect to the baseline values.

- Pain intensity difference (PID)

PID between baseline and first daily home VAS measurement at day 6 (PID) was significant in both therapeutic groups. PID was 27.3 mm VAS and 29.5 mm VAS in IR-TPFC and SR-TPFC group, respectively (Figure 2). The 95% CI of the difference between the two groups was [-3.13, 7.5].

Figure 2: PID between the baseline and day 6 (mm VAS)



- Cumulative pain intensity (CPI) differences

At days 2, 3, 6, 8 and 15 patients measured pain intensity at different times of the day which was later summed up per day for the statistical analysis purposes. During the course of treatment a significant reduction of daily CPI was observed from 271.2 mm to 168 mm in IR-TPFC group and from 277.6 mm to 160.5 mm. There were no significant differences between the two groups (Table 1).

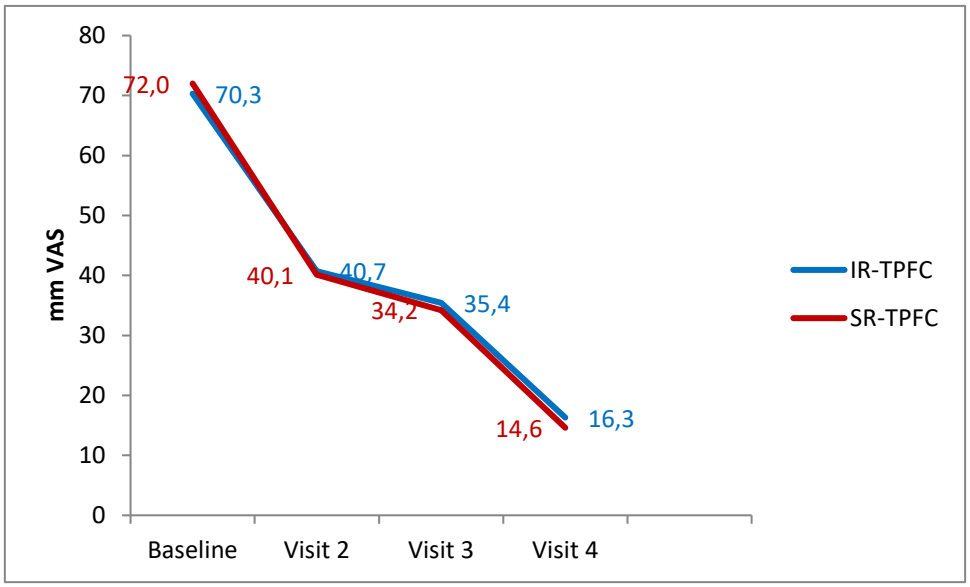
Table 1: CPI differences (mm VAS)

	IR-TPFC (mean values [mm])	SR-TPFC (mean values [mm])	Difference between IR-TPFC and SR-TPFC		Test of equality
			Estimates	Confidence interval	
CPI d2	271.2	277.6	-6.4	[-25.99, 13.16]	non-sig.
CPI d3	235.1	238.3	-3.2	[-23.26, 16.84]	non-sig.
CPI d6	185.8	189.5	-3.7	[-27.11, 19.72]	non-sig.
CPI d8	201.5	196.3	5.2	[-20.35, 30.83]	non-sig.
CPI d15	168.0	160.5	7.4	[-22.77, 37.63]	non-sig.

- Office pain intensity differences (PID 2, PID 3 and PID 4)

At each visit VAS measurements were done and difference calculated with respect to baseline value. The 3 endpoints analysis revealed a significant reduction of around 30 mm at Visit 2, approximately 35 mm at Visit 3 and approximately 55 mm at Visit 4. No statistical significant difference was detected between the treatment groups (Figure 3).

Figure 3 Pain intensity at Visits 2, 3 and 4 (mm VAS)

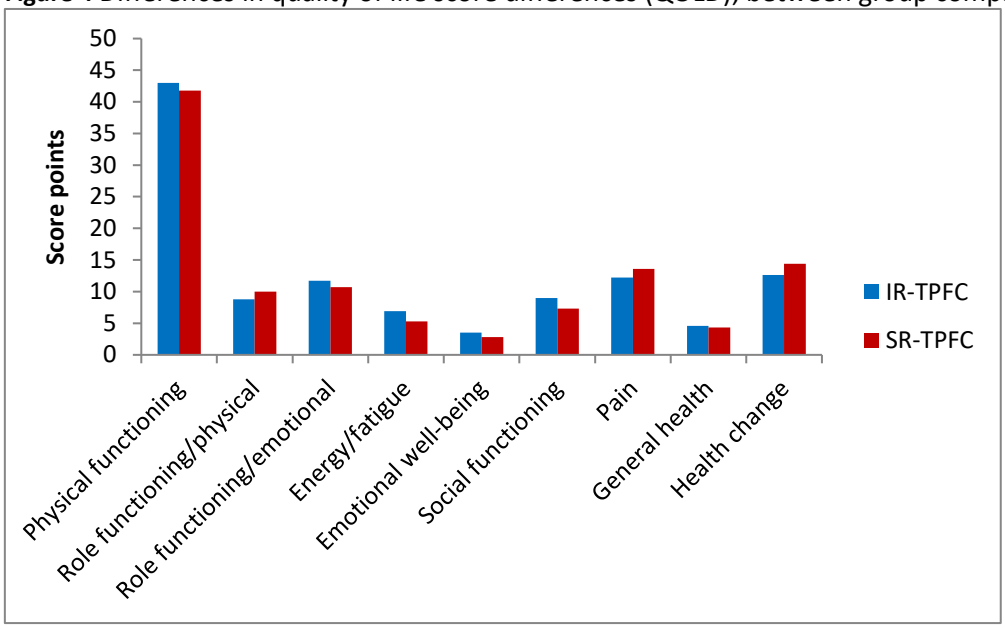


- Quality of life score difference (QOLD)

Nine endpoints were formed from the questionnaire of different entities of every day's life and the Quality of life related to them. Differences were calculated from the measurements at Visit 4 and at baseline.

In all the categories measured the Quality of life was significantly improved (higher scores at Visit 4 compared to baseline values) with no significant difference between the two therapeutic groups.

Figure 4 Differences in quality of life score differences (QOLD); between group comparison



- Difference in Pain Interference Score and related endpoints (dPIS)

There were 21 endpoints analysed based on questionnaire assessing seven categories of pain interference with usual daily activities at each of the study visits and difference between baseline and Visits 2, 3 and 4.

The pain interference has been significantly reduced compared to baseline values in all the categories at all the Visits (Figures 2, 3 and 4). Despite relatively consistent trend towards greater efficacy of SR-TPFC, no significant difference was found between the two groups.

Figure 5 Pain interference scores reduction at Visit 2 (dPIS 2); between groups comparison

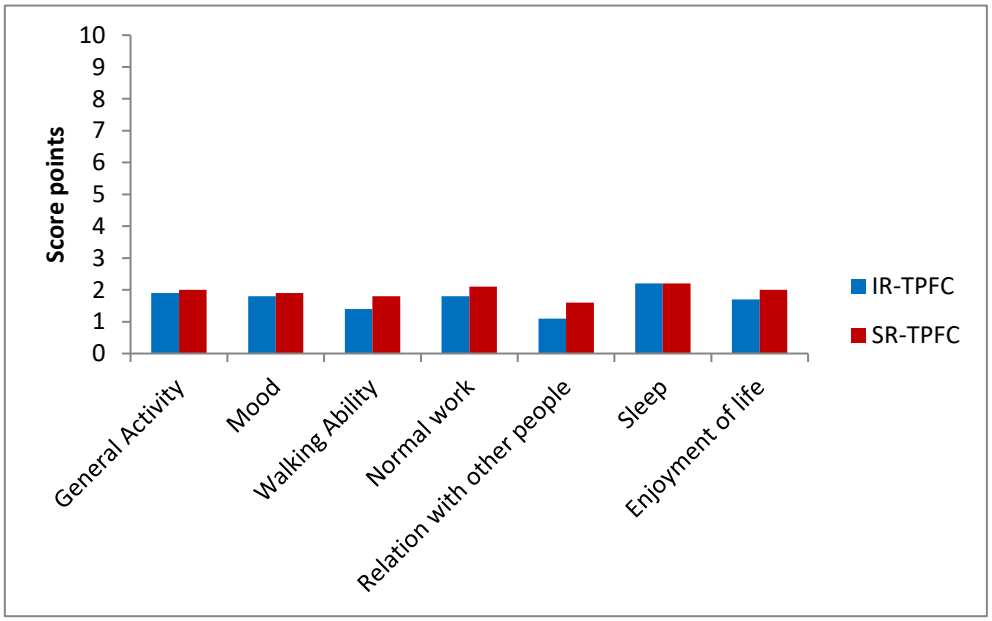


Figure 6 Pain interference scores reduction at Visit 3 (dPIS 3); between group comparison

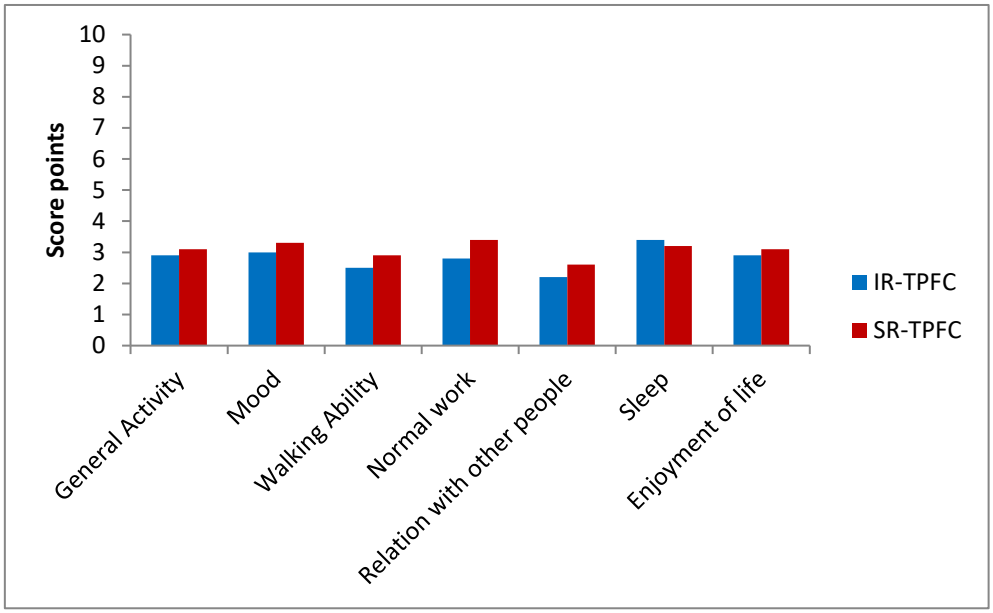
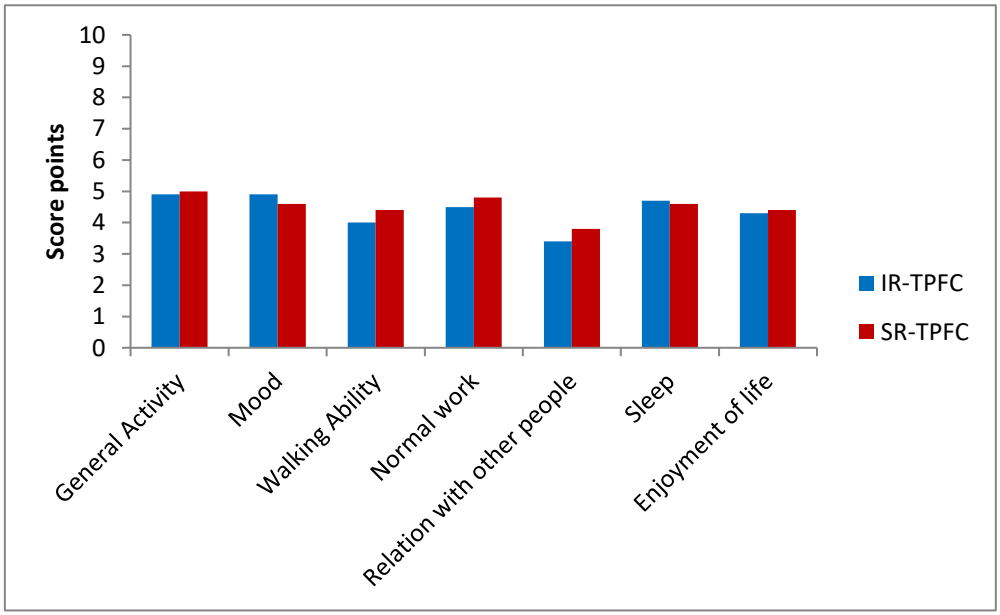


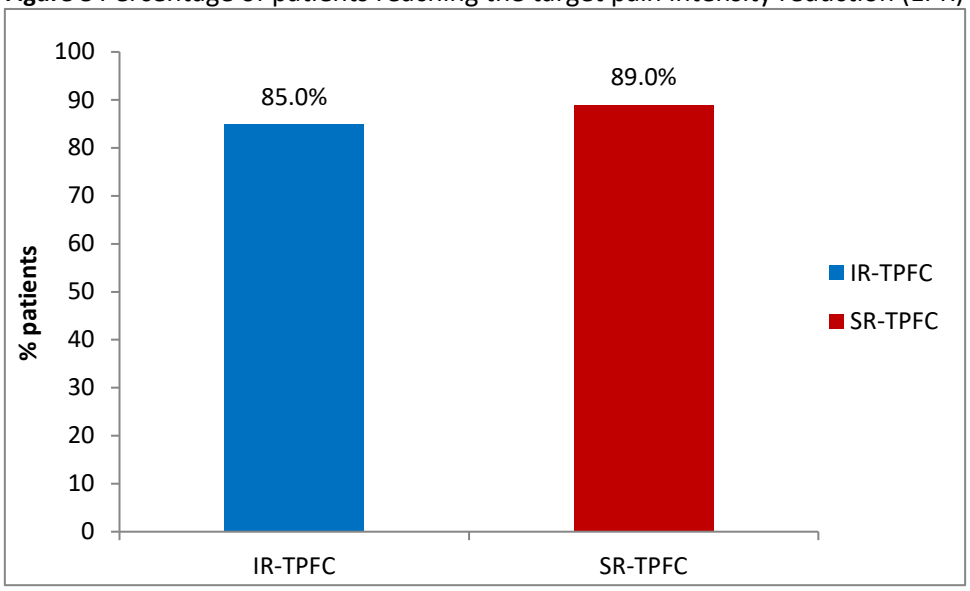
Figure 7 Pain interference scores reduction at Visit 4 (dPIS 4); between group comparison



- Percentage of patients with excellent response (EPR)

Altogether 85.0% of patients taking IR-TPFC and 89.0% of those taking SR-TPFC have achieved excellent response defined by a VAS score reduction to 30 mm or less or at least 50% VAS score reduction with respect to baseline. The reference visit was at the end of therapy for a particular patient. There was no significant difference between the two groups.

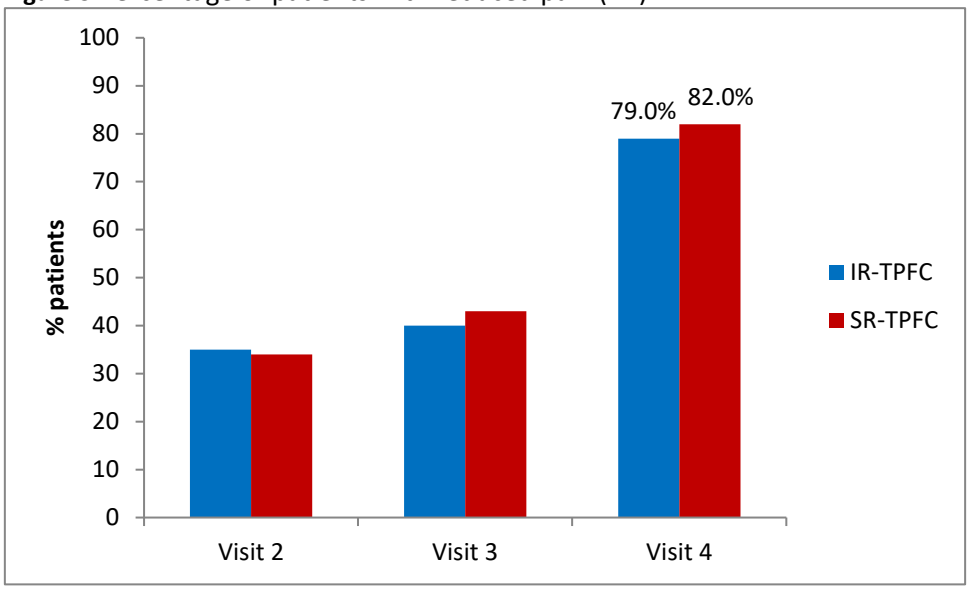
Figure 8 Percentage of patients reaching the target pain intensity reduction (EPR)



- Percentage of patients with reduced pain (RP)

Besides the end-therapy Visit which was assessed by primary endpoint the percentage of patients reaching the therapeutic goal of the pain reduction to 30 mm VAS was also analysed for Visits 2, 3 and 4. Hence, three endpoints have been yielded in this respect. The percentage of such patients significantly increased from Visit 2 to Visit 3 and from Visit 3 to Visit 4 when increased up to 79.0% in the IR-TPFC and 82.0% in the SR-TPFC group. The 95% CI and P value at each of the visits indicated no difference between the two therapeutic groups.

Figure 9 Percentage of patients with reduced pain (RP)

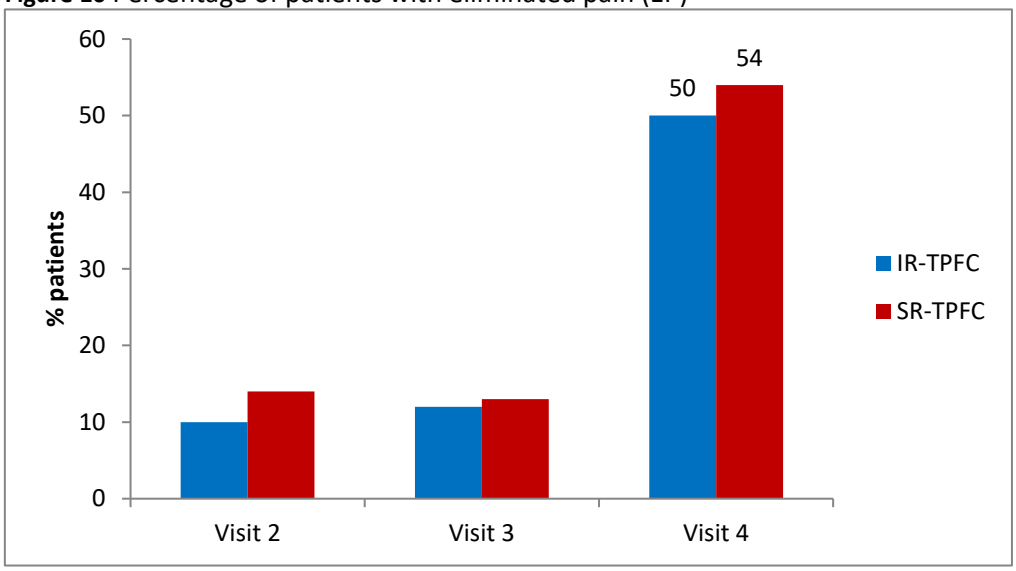


- Percentage of patients with eliminated pain (EP)

These 3 endpoints were calculated as proportion of patients reaching the target pain reduction to less than 10 mm VAS. The endpoints related to measurements in the office at Visits 2, 3 and 4. Similarly, to previous

endpoints, the increase of eliminated pain percentages was observed, reaching 50% in the IR-TPFC and 54% in SR-TPFC at Visit 4 (Figure 10). Again no significant difference between the two groups was identified.

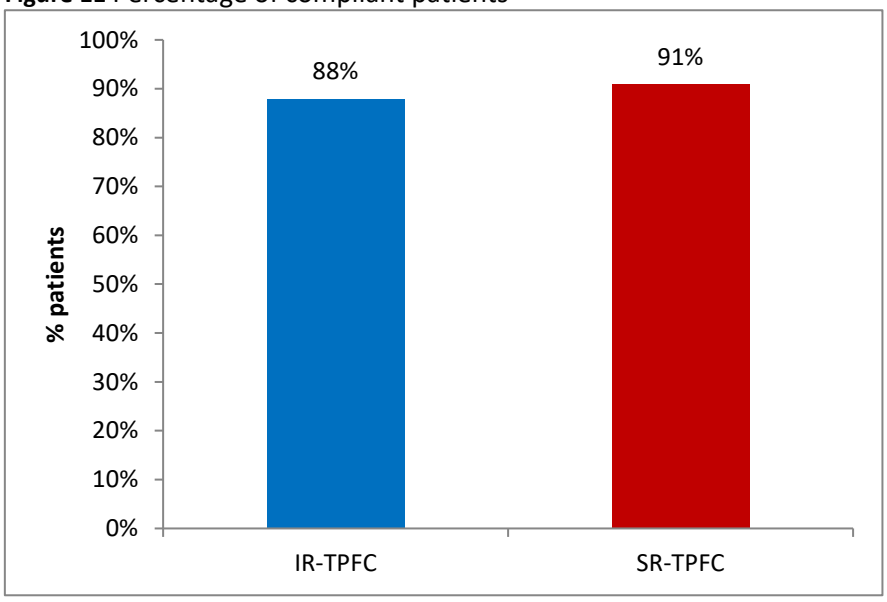
Figure 10 Percentage of patients with eliminated pain (EP)



- Percentage of compliant patients

This endpoint was defined as the percentage of patients having a drug intake compliance of more than 80% at the end therapy visit. It has been shown that there were 88% and 91% percentage of patients compliant in IR-TPFC and SR-TPFC group, respectively (Figure 11). There was no significant difference between the therapeutic groups.

Figure 11 Percentage of compliant patients



Efficacy conclusions

The efficacy analysis tackled pain intensity reduction, improvement of QOL and interference of pain with daily activities. The intensity of low back pain was significantly reduced during the course which led to significant improvement of QOL and reduction of pain impact on daily activities.

Primary efficacy endpoint demonstrated that nearly 80% of patients in IR-TPFC and 84% in SR-TPFC group had clinical meaningful reduction of low back pain. The difference between the two therapeutic groups was not significant which denotes that low back pain reducing effect of SR-TPFC was not inferior to the IR-TPFC. The result of primary endpoint correlated with the results of wide array of secondary endpoints which all demonstrated significant improvement of both therapies with no significant differences between the two therapies. Furthermore, in terms of compliance with the therapy, average patient compliance was more than 90% with no evident difference between the two groups. The usages of rescue medicines decreased during the clinical trial in both therapeutic groups.

SAFETY RESULTS

The average exposure to the study drug treatment per patient was 20,7 days with 21.2 days in the IR-TPFC groups and 20.2 days in the SR-TPFC group.

There were altogether 271 adverse reactions (AR) appearing in 127 patients representing 40.6% of entire patient population. Altogether, 137 AR appeared in 64 patients in IR-TPFC group and 134 were reported in 63 patients in SR-TPFC group. Overall incidence of AR, expressed as the number of patients with at least one AR was 41% and 40% in SR-TPFC and IR-TPFC group, respectively. The 95% CI for the proportions included zero point and the difference was not significant between the two therapeutic groups (Table 2).

Table 2 Overall incidence of adverse reactions

	Yes		**No**		**total**	
	N	%	N	%	N	%
All patients	127	41%	186	59%	313	100%
IR-TPFC	64	41%	93	59%	157	100%
SR-TPFC	63	40%	93	60%	156	100%
Confidence interval for difference of proportions of patients with yes			[-0.111,0.12]		p > 0.05	

The adverse reactions appearing in more than 1% of patients are displayed in the Table 3.

Table 3 Adverse reaction listing by type with the incidence of 1% or more in the entire study population

	IR-TPFC		SR-TPFC		Total	
	number of different patients with reaction	percentage with respect to all patients	number of different patients with reaction	percentage with respect to all patients	number of different patients with reaction	percentage with respect to all patients
Patients with any adverse reaction	64	40.8%	63	40.4%	127	40.6%
Nausea	30	19.1%	28	17.9%	58	18.5%
Dizziness	24	15.3%	20	12.8%	44	14.1%

Constipation	21	13.4%	21	13.5%	42	13.4%
Somnolence	10	6.4%	11	7.1%	21	6.7%
Vomiting	10	6.4%	7	4.5%	17	5.4%
Dry mouth	5	3.2%	3	1.9%	8	2.6%
Abdominal pain	2	1.3%	6	3.8%	8	2.6%
Headache	3	1.9%	4	2.6%	7	2.2%
Dyspepsia	3	1.9%	3	1.9%	6	1.9%
Hyperhidrosis	3	1.9%	1	0.6%	4	1.3%
Sleep disorder	2	1.3%	2	1.3%	4	1.3%
Fatigue	1	0.6%	3	1.9%	4	1.3%
Decreased appetite	1	0.6%	3	1.9%	4	1.3%
Paraesthesia	3	1.9%	0	0.0%	3	1.0%
Flatulence	2	1.3%	1	0.6%	3	1.0%
Chest pain	2	1.3%	1	0.6%	3	1.0%

As for the four safety endpoints encompassing the incidence of four common AR expected to occur with the tested drugs, nausea was the commonest followed by dizziness, constipation and vomiting. The differences in these four AR were not significant between the two treatments (Table 4).

Table 4 Comparative incidence of nausea, dizziness, constipation and vomiting

	IR-TPFC		SR-TPFC		CI for diff. of proportions of patients with adverse reaction	
	N	%	N	%		
Nausea	30	19.1%	28	17.9%	[-0.075,0.106]	p > 0.05
Dizziness	24	15.3%	20	12.8%	[-0.059,0.111]	p > 0.05
Constipation	21	13.4%	21	13.5%	[-0.08,0.08]	p > 0.05
Vomiting	10	6.4%	7	4.5%	[-0.038,0.075]	p > 0.05

There were altogether nine patients prematurely excluded on account of adverse reactions. Two of them were taking IR-TPFC and had altogether 7 AR, and 7 patients with 21 AR were in SR-TPFC therapeutic group. There were total of 28 adverse reactions involved with maximum 5 AR per patient. The difference was not statistically significant (Table 5).

Table 5 Proportion of patients prematurely excluded due to clinically significant adverse reaction

	Yes		No		total	
	N	%	N	%	N	%
All patients	9	3%	304	97%	313	100%
IR-TPFC	2	1%	155	99%	157	100%
SR-TPFC	7	4%	149	96%	156	100%
CI for diff. of proportions of patients with yes:			[-0.08,0.012]		p > 0.05	

Further comparative analysis of severity, frequency, therapeutic intervention, outcome and expectedness did not reveal any differences between the groups.

There were no serious adverse events and no symptomatic overdose in this study.

Safety conclusions

The two therapies had similar safety profile. Most common ARs were nausea, dizziness, constipation and vomiting. The overall incidence as well as the incidence of most common ARs was not different among the two groups. There were no significant differences neither in the number of excluded patients on account of safety nor with respect to different types of ARs.

CONCLUSIONS

In open randomised clinical trial KCT03/2015 (acronym Treasure) in patients with acute low back pain two formulations of fixed dose combination of paracetamol and tramadol were analysed.

In terms of efficacy, results demonstrated significant improvement in multiple endpoints encompassing pain reduction, pain interference and quality of life. The SR formulation of tramadol/paracetamol fixed combination compared to IR formulation showed similar efficacy with a non-inferior analgesic action of the former has been proven. The primary endpoint, set up to demonstrate efficacy of both formulations, has proven high efficacy as nearly 80% of patients in IR-TPFC and 84% in SR-TPFC group reached clinical meaningful reduction of pain. Furthermore, results of primary endpoint denote statistically significantly adequate efficacy of SR formulation in comparison with IR formulation. Likewise, by all of the secondary efficacy endpoints (including differences in pain intensity at all control visits, cumulative pain intensity throughout the dosing interval, quality of life difference, pain interference score difference, proportion of patients with excellent pain response, proportion of patients with reduced pain, proportion of patients with eliminated pain) was proved a significant improvement between the values at baseline and at the end of the trial. Comparing results of secondary endpoints between IR and SR formulation, there was no difference between two therapeutic groups. High proportion of patients was compliant in both therapeutic groups with no significant differences detected.

Safety profile analysis showed similar safety profile of the two formulations. No serious events were reported in this study.