Efficacy and Safety of Tramadol Hydrochloride/Paracetamol in Patients with Moderate to Severe Acute Low Back Pain - TREASURE

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Abstract

Objective: To evaluate the efficacy, safety and effects on the quality of life (QoL) of immediate release 37.5 mg/325 mg (IR T/P) and sustained release tramadol/paracetamol 75 mg/650 mg (SR T/P) tablets in patients with moderate to severe acute low back pain (aLBP).

Methods: This was a randomized, open-label, prospective, two-arm study in adults with moderate to severe aLBP (symptom duration ≤ 12 weeks, pain intensity ≥ 40 mm on the Visual Analogue Scale (VAS)). Patients were treated with 4-times daily IR T/P 37.5 mg/325 mg or 2-times daily SR T/P 75 mg/650 mg for up to 4 weeks. The primary endpoint was the percentage of patients with pain intensity reduced to ≤ 30 mm on VAS at therapy conclusion. Secondary endpoints included pain intensity differences, cumulative pain intensity, QoL, pain interference with activities of daily life and proportions of patients with an excellent response. Safety was assessed by adverse events monitoring.

Results: The results presented are limited to the IR T/P arm, as the products containing modified-release paracetamol were suspended from markets in Europe. Out of 157 patients treated with IR T/P target reduction of pain intensity was observed in 79.6% of them. Pain intensity decreased from 70.3 mm on VAS at baseline to 16.3 mm at endpoint. Improvements in all domains of QoL and pain interference with activities of daily life were noted. Treatment was safe and well tolerated.

Conclusion: IR T/P 37.5 mg/325 mg is effective and safe in relieving moderate to severe aLBP. Good pain control with this combination was accompanied by markedly reduced pain-related interference with the activities of daily living and improved QoL.

Keywords: *low back pain, tramadol, paracetamol, efficacy, quality of life, pain interference, safety*

Introduction

Low back pain is an important clinical and public health issue (1). It is the most frequent medical condition after common cold and one of the most frequent causes of visits to a family doctor, experienced by up to 80% of all people at some point in their lifetime (1-3). While it is often resolved in the short-term (1-3 months), it continues to be an issue in a sizeable proportion of patients, who report reoccurrences of LBP episodes or persisting disabling symptoms (2). It is a well-known fact that the incidence of LBP is the highest in working age adults, making it a major cause of activity limitation and work absence globally (1,4). The longer the patients are unable to work, the higher the number of visits to physicians and the higher the costs for public health systems (5). Clearly consequences are not evident

only at individual's level, but also impose a high burden on families, communities, the industry and governments (6). Back pain can reduce engagement and participation of a patient in all areas of daily life, thus having a profound effect on the quality of life (7). Therefore, it is of utmost importance that recovery of these patients is both efficient and as quick as possible.

Apart from patients' education and advice on returning to normal activities while avoiding bed rest, which was the focus of recent guidelines on back pain, a pivotal part of managing back pain is early and effective analgesia (8). The role of pharmacological management is to provide a symptomatic relief of acute pain in order to enable the patients to continue or recommence their normal daily activities (9,10).

Although non-steroidal anti-inflammatory drugs (NSAIDs) have been the main pharmacological treatment of acute and chronic pain in several indications, they might not be the optimal choice for a sizable proportion of patients. Along with the fact that many receive inadequate pain relief with NSAIDs, their use can be associated with various adverse events, among which gastrointestinal and cardiovascular are the most important ones (11). Therefore, a combination of weak opioid tramadol and a simple analgesic such as paracetamol is of interest. The combination of tramadol and paracetamol (T/P) brings together two well-known analgesics that target multiple sites of pain pathways. Their complementary mechanisms of action produce synergistic and enhanced analgesia, allowing reduction of the required dose as compared with an equally effective dose of each component alone. Therefore, the combination has a relative safety advantage with reduced potential for adverse reactions of each component, offering an improved benefit/risk ratio. Moreover, the onsets of analgesia are different and complement each other, since paracetamol alone acts earlier than tramadol, while tramadol has a relatively slow onset of action and a longer half-life; this in turn provides both - rapid and sustained analgesia (11-13). The T/P combination has demonstrated good pain control in many patients with acute and chronic pain and is a treatment option according to several guidelines, including those for osteoarthritis, postoperative pain and LBP (12,14).

The present 4-week study aimed to evaluate the analgesic efficacy, safety and effects on the quality of life (QoL) of immediate release T/P 37.5 mg/325 mg and sustained release T/P 75 mg/650 mg oral single pill combination in patients with moderate to severe aLBP. In 2018, all products containing modified-release paracetamol were suspended from the European market (15). For that reason, the results presented in this article are limited to immediate release T/P formulation.

Patients and methods

Patients. Men and women between the age of 18 and 75 years, with previously treated or untreated aLBP (symptom duration ≤ 12 weeks) of moderate to severe intensity at baseline (average pain intensity score on the horizontal Visual Analog Scale (VAS) ≥ 40 mm over 48 hours prior to screening), were eligible for the study.

Drugs that might have influenced the final treatment effect of the tested substances (e.g. other analgesics, anesthetics, muscle relaxants) was prohibited during the study. Other exclusion criteria included: concomitant use of neuroleptics or drugs for seizures, sedative hypnotics, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, pregnancy, lactation or breastfeeding, severe hepatic impairment, unstable angina pectoris, acute myocardial infarction within 4 weeks prior to the screening visit, any diagnosed mental disorder, known or suspected alcohol or drug abuse or addiction within three years preceding the screening. The patients undergoing surgical procedures during the study period or patients who under investigator's opinion would not be compliant to the treatment were also excluded.

The trial and all of the amendments were reviewed by Independent national Ethics Committees in all participating countries. To participate in the study, the study was explained in depth to all potential participants, and all patients needed to provide written informed consent before enrollment. The study was conducted in accordance with the ethical principles based on the Declaration of Helsinki.

Study design and interventions. This was a 4-week, randomized, open-label, prospective, two-arm, multicenter, phase IIIb/IV clinical study conducted at 25 sites in Slovenia, Poland, Croatia and the Czech Republic. Patients were randomly assigned in 1:1 ratio to receive immediate release T/P 37.5 mg/325 mg film-coated tablets (Doreta®, Krka, d.d., Novo mesto) q.i.d (1 tablet every 6 hours) or T/P 75 mg/650 mg sustained release tablets (Doreta SR®, Krka, d.d., Novo mesto) b.i.d. (1 tablet every 12 hours). Overall treatment duration was 1 to 4 weeks. During treatment period, patients were allowed to take naproxen sodium 550 mg film-coated tablets (Nalgesin® forte, Krka, d.d., Novo mesto) max. twice daily as a rescue medication (in case sufficient pain relief was not achieved with the study medication). In patients taking naproxen, pantoprazole 20 mg (Nolpaza®, Krka, d.d., Novo mesto) once daily was permitted for gastric protection.

Patients were seen at baseline visit (V1), when the screening procedure was carried out, and treatment was initiated in eligible patients. Participants were assessed on up to 3 additional control visits during the study period; at Day 7 (V2), Day 14 (V3) and Day 28 (V4) after initiation of the therapy. Additionally, participants were requested to complete patient's diaries on Days 2, 3, 6, 8 and 15. If a patient reached the target reduction of pain as a criterion of successful treatment, the investigators had an option to stop the treatment sooner than planned i.e. before 28 days after the initiation. Nevertheless, all patients were obliged to attend the final visit on day 28 for the end-of-study assessment.

Outcome measures. The primary efficacy endpoint was to determine the proportion of patients with clinically meaningful improvement of LBP. Reduction of LBP intensity was considered to be clinically meaningful if pain intensity ≤ 30 mm on VAS was achieved on the day of therapy conclusion (i.e. on any of the control visits). Secondary efficacy endpoints included pain intensity difference scores (PI-d), cumulative pain intensity (CPI), and the proportions of patients with the following responses to therapy: excellent response, eliminated pain. Also, pain interference with the activities of daily living and QoL outcomes were evaluated as secondary endpoints.

Pain intensity was determined on VAS which is basically a horizontal 100 mm line with anchors "no pain" on the left end and "the worst pain one can imagine" on the right end. A patient makes a mark on the line assessing his/her level of pain, and distance from that mark to the left end (in mm) actually represents the level of pain. Assessments were made at baseline and at each of the consecutive visits and were self-recorded by the patient using a diary. PI-d scores were determined as the difference between the result on VAS at each control visit and baseline. Additional PI-d score was calculated as the difference in pain intensity at the beginning of Day 6 (recorded by the means of patient diary), and the respective value at baseline. CPI was evaluated by the sum of 5 daily home VAS scores using the patient's diary at defined days (thus ranging from 0-500 mm on VAS each day). Excellent pain response was defined by VAS score reduction to ≤30 mm or ≥50% reduction of pain on the day of therapy discontinuation with respect to the baseline value, while reaching VAS <10 mm was considered as eliminated pain. Interference of pain with the activities of daily living was evaluated during a visit on the basis of the short form of Brief Pain Inventory (BPI). BPI evaluates the interference of pain on the patient's functioning relative to seven activities (general activity, mood, walking ability, normal work, relations with other people, sleep, enjoyment of life) on a scale from 0 to 10 (0 = no interference to 10 = interferes completely); a lower score indicates less interference. BPI score was determined individually for each activity at baseline and each control visit. QoL was assessed at baseline and at the

final visit by means of the 36-Item Short Form Health Survey (SF-36). SF-36 evaluates nine domains of QoL (physical functioning, physical and emotional role functioning, energy/fatigue, emotional well-being, social functioning, pain, general health, health change) on a scale from 0 to 100 (0 = worst state; 100 = best state), with a positive difference indicating improvement. The proportion of compliant patients was also one of the secondary endpoints and was assessed by counting the pills and treatment days and a subsequent calculation according to the standard drug compliance equation. A patient was considered to be compliant if he/she took more than 80% of all doses (measured at the end-therapy visit).

Safety was assessed by monitoring the incidence and severity of adverse events (AEs) throughout the study. AE reporting was made using patient diary forms (at same points as VAS measuring) and safety assessment was carried out at each control visit (by interview and physical examination, if needed). Short-term tolerability of treatments was evaluated also by monitoring the incidences of four common adverse reactions (nausea, dizziness, vomiting and constipation), which were further analyzed as separate endpoints.

Statistical analyses.

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 a comparison between the treatment groups, a set of 250 per-protocol patients in both groups was deemed adequate. To assess the 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 AEs. For comparative analyses associated with AEs, 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 imputation 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 the confidence interval. No corrections for multiple comparisons were made.

Results

Of 316 patients screened, 313 patients were randomized to receive either IR T/P 37.5 mg/325 mg (N=157) or SR T/P 75 mg/650 mg (N=156). Since all the products containing modified-release paracetamol were suspended from the European market in 2018 (15), the results presented are based solely on the data collected from 157 patients included in the IR T/P group. All patients in the IR group took at least one dose of the study medications, thus representing a safety population that coincides with the ITT set.

Demographic and baseline characteristics of study participants are summarized in Table 1. At baseline evaluation the patients reported average LBP duration of 14.8 days. 61% of patients had been previously treated (in the last 12 months) for this indication; most of them with NSAIDs and/or opioids (93.8%).

Table 1: Demographic and baseline characteristics (ITT population, randomized to IR T/P 37.5 mg/325 mg)

Characteristic	ITT IR group (N = 157)
Age, years, *mean (SD)*	50.2 (13.6)
Gender, n (%) *female* *male*	 94 (60%) 63 (40%)
Body mass index, kg/m^2, *mean (SD)*	27.2 (4.4)
Concomitant conditions[a], n (%) *None* *Cardiovascular diseases* *Allergy* *Diabetes* *Asthma/COPD* *Depression* *Other*	 60 (38%) 56 (36%) 17 (11%) 16 (10%) 6 (4%) 1 (1%) 68 (43%)
Duration of current LBP episode, days, *mean (SD)*	14.8 (16.8)
Treatment of LBP in last 12 months *yes* *no*	 96 (61%) 61 (39%)
Baseline pain intensity, VAS (mm), *mean (SD)*	70.3 (13.0)

ITT - intention-to-treat, IR – immediate release, SD - standard deviation, COPD - chronic obstructive pulmonary disease, LBP - low back pain, VAS – Visual Analogue Scale

[a] Patient could have more than one concomitant medical condition; percentages are relative to all patients in ITT population (N=157)

Efficacy results

In the analysis of efficacy we assessed pain intensity reduction, improvement of QoL and interference of pain with daily activities. With regard to the primary efficacy endpoint, namely the percentage of patients reaching target reduction of pain intensity (VAS ≤ 30 mm) 79.6% patients achieved that goal.

The result of primary endpoint correlated well with the results of wide array of secondary endpoints which all demonstrated significant improvements. Mean pain intensity scores gradually decreased throughout the study period, from 70.3 mm pain intensity on VAS at baseline to 16.3 mm at the final visit (Figure 1). These results were consistent with those obtained from patients' diaries, which demonstrated a change in CPI mean score from 271.2 mm at Day 2 to 168.0 mm at Day 15. Even the first pain intensity evaluation recorded by patients' diaries at the beginning of Day 6 demonstrated a significant reduction of pain intensity from baseline (-27.3 mm; PI-d between Day 6 and baseline). This correlated well with pain intensity evaluation on the first control visit at Day 7, where more than 40% (-29.7 mm; PI-d between V2 and baseline) pain reduction from baseline was observed.

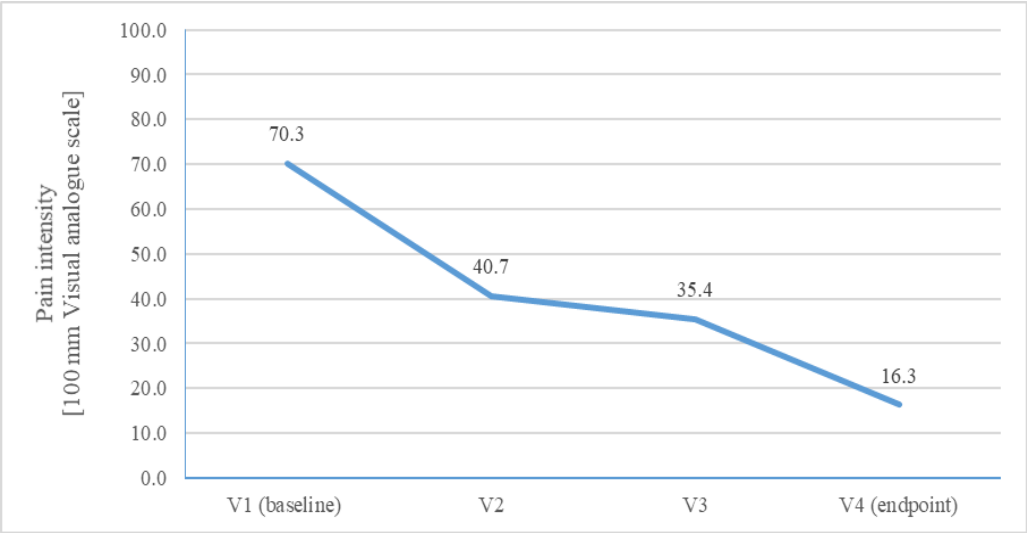

Figure 1: Mean pain intensity in patients treated with IR T/P 37.5 mg/325 mg as measured on VAS [mm] at baseline and each control visit

There were 58 patients (37.5%) who were early concluders, reaching the primary efficacy endpoint earlier than at the 4-week mark. Sixty percent of them (35 patients) concluded the therapy already by Day 7 (V2). Excellent pain response, namely VAS score ≤ 30 mm or VAS score reduction > 50% on the day of therapy conclusion, was reported by 85% of patients. At endpoint, 50% of patients reported eliminated pain (≤ 10 mm on VAS).

At the end of observation, pain interference with daily activities was markedly reduced compared to baseline in each of the seven activities defined by the BPI score (Table 2). Significant improvements were observed already at V2 and consistently improved each subsequent week. The patients experienced reductions in interference of pain particularly with mood and sleep (relative to baseline, score improvements for almost 80%). In absolute terms, the greatest mean score difference was noted for interference with the general activity (-4.88), which scored highest at baseline (i.e. determined as activity most affected by pain).

Table 2: Mean BPI scores for pain interference with the activities of daily life in patients treated with T/P 37.5 mg/325 mg at baseline and each control visit

	Mean (SD) BPI score			
BPI item	Baseline (n=157)	V2 (n=156)	V3 (n=115)	V4 (endpoint) (n=148)
General activity	6.95 (2.07)	5.04 (2.36)	4.20 (2.30)	2.07 (2.46)
Mood	6.28 (2.43)	4.44 (2.63)	3.50 (2.47)	1.42 (1.97)
Walking ability	5.65 (2.43)	4.30 (2.55)	3.48 (2.26)	1.69 (2.45)
Normal work	6.43 (2.06)	4.67 (2.50)	3.90 (2.37)	1.93 (2.46)
Relations with other people	4.61 (2.59)	3.52 (2.45)	2.73 (2.45)	1.26 (2.02)
Sleep	6.00 (2.53)	3.82 (2.65)	2.98 (2.51)	1.31 (2.11)
Enjoyment of life	5.84 (2.88)	4.12 (2.87)	3.21 (2.62)	1.50 (2.25)

BPI – Brief Pain Inventory; SD – standard deviation

SF-36 domain scores at baseline and final visit are presented in Figure 2. The results demonstrated significant improvements in all nine domains of QoL. As reflected by the mean (SD) score difference of 43.0 (33.3) points, treatment with T/P provided the greatest improvements in physical functioning; smaller effects were noted in the domain of emotional well-being.

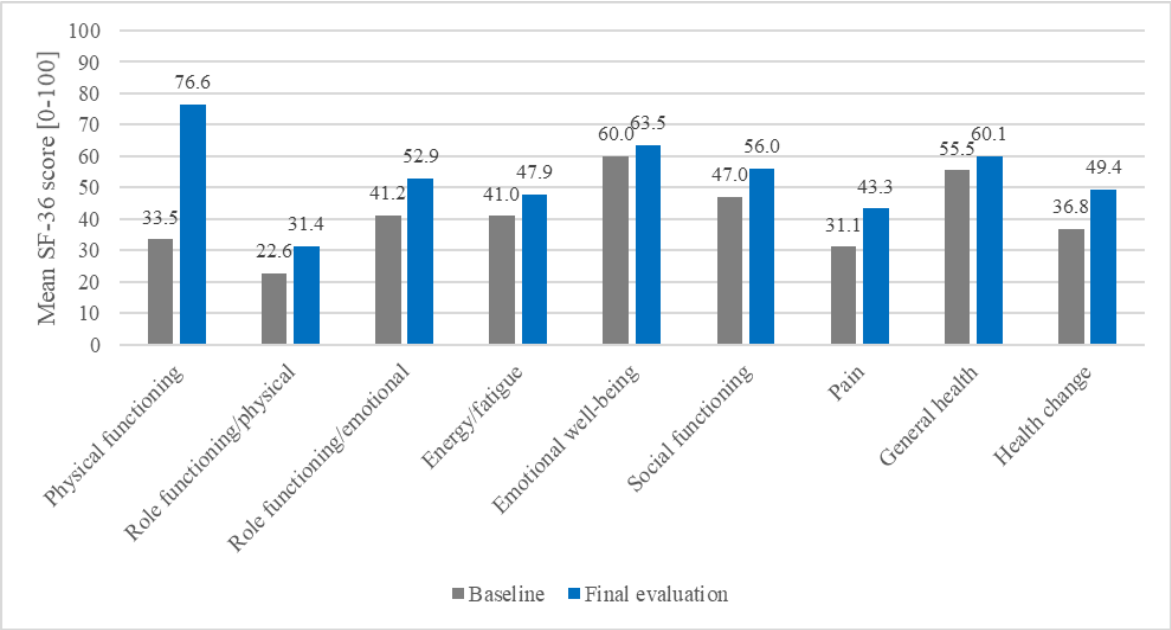

Figure 2: Mean SF-36 scores in patients treated with T/P 37.5 mg/325 mg at baseline and final evaluation for 9 QoL domains

The usage of rescue medicines was overall low, taken by less than one quarter of patients, with a constant decreasing trend throughout the study period. The proportion of patients requiring a rescue medicine decreased from 23.6% in the first period (before V2) to 14.6% in the period between V3 and V4. In terms of therapy compliance, the mean percentage of compliant patients was 88%.

Safety results

More than half of patients (57.3%) in the safety population of the IR group did not report any AE during the study; there was no data available for one patient. The most commonly reported adverse reactions (i.e. drug-related adverse events; AR) during all study periods were nausea (reported by 19.1% of patients), dizziness (15.3% of patients), constipation (13.4% of patients), somnolence and vomiting (both reported by 6.4% of patients). As presented in Table 3, the proportion of patients who reported ARs was the highest (34.4%) in the 1st period (between baseline and V2), and decreased during the study to 10.2% of patients with AR in the last period (between V3 and V4). Exception was constipation, the occurrence of which was the highest in 2nd period (between V2 and V3). In majority of patients (76.6%) with ARs, these were categorized as mild. Only one patient experienced severe AR, which occurred in the 1st period of the study and was the reason that patient withdrew the medicine. Apart from that, there was one additional withdrawal due to moderate AR, also occurring in the 1st period. There were no serious adverse events.

Table 3: Occurrences of the most commonly reported ARs under T/P 37.5 mg/325 mg by study period (safety population)

Event[a]	Patients, n (%)[b]		
	1st period (V1-V2)	2nd period (V2-V3)	3rd period (V3-V4)
Patient with any adverse reaction	54 (34.4%)	22 (14.0%)	16 (10.2%)
Nausea	28 (17.8%)	5 (3.2%)	4 (2.5%)
Dizziness	22 (14.0%)	2 (1.3%)	3 (1.9%)
Constipation	9 (5.7%)	11 (7.0%)	6 (3.8%)
Somnolence	10 (6.4%)	3 (1.9%)	3 (1.9%)

Vomiting	9 (5.7%)	1 (0.6%)	0 (0.0%)

[a] Sorted by occurrences throughout the whole study period.

[b] Each patient is counted once for every different AR they had experienced.

Discussion

The efficacy of the oral single pill T/P (37.5 mg/325 mg) combination was assessed in several well designed studies with moderate to severe pain due to dental, abdominal, orthopedic or hand surgery, as well as in patients with musculoskeletal pain, painful diabetic peripheral neuropathy or migraine pain (16). As for musculoskeletal pain the efficacy of a single pill combination was confirmed in trials versus placebo and/or other analgesics as short-term (17,18), longer-term (≤ 3 months) (19-21), or as add-on therapy (22,23).

Due to the suspension of all products containing modified-release paracetamol from the European market in 2018 (15), this article will present the efficacy and safety of IR T/P solely. In this 4-week study, the mean baseline pain scores were at the upper level of moderate pain, i.e. 70.3 mm (range 40-100 mm). Therapy with IR T/P 37.5 mg/325 mg resulted in significant pain reductions, as clinically meaningful improvement of LBP (VAS ≤ 30mm) was obtained in almost 80% of patients. There are many ways to assess the efficacy of an analgesic. The one chosen in this study is a variance of the widely accepted minimal clinically important difference, and is recommended as one of the primary endpoints in the latest guidelines on pain treatment (24). This concept is more relevant than a statistically significant difference, because pain is particularly subjective, and pain decrease that is statistically significant may not be actually significant to the patient (25). Therefore, it was used as a crucial criterion for the evaluation of drug efficacy in the population of patients with aLBP.

There was a variety of several secondary endpoints, which additionally confirmed the high efficacy of the therapy and were in line with the efficacy results obtained in other studies. Significant reductions in mean pain intensity were seen early, as 40% reductions in mean pain intensity were seen already in the first week of therapy. Nevertheless, regular therapy clearly provided additional improvements, as mean pain intensity decreased to 16.3 mm on VAS (-24.4 mm additionally from V2) at final visit. Furthermore, there was a meaningful proportion of patients with excellent pain relief. The latter was reported by 85% of patients, while half of the patients reported eliminated pain. Patients' diary VAS scores are particularly valuable, because they are measured in real-time and in the patient's natural environment. Therefore, the patient's diary is considered to be more accurate than the data obtained by recall (26). In this study cumulative pain intensity was exclusively measured by the patient's diary, at home. The pain decreased from 271.2 mm at Day 2 to 168.0 mm at Day 15, which corresponds to a reduction of more than 35%. It is difficult to determine which of the endpoints is more relevant to clinical practice. For instance, in a recent systematic review the authors suggested that pain relief (calculated using total pain relief) may be more sensitive to treatment effects with higher standardized effect sizes compared to the summed pain intensity difference (27). In general, effect sizes ranging from 30% to 50%, especially when pain is halved (50%), considered as substantial pain relief are used in clinical trials (28).

It is a well-known fact that pain has a broad impact on people's lives, making improvements of pain-related QoL and interference with daily activities important treatment issues (29). Evaluation of these issues was performed using validated questionnaires, SF-36 and BPI, which showed that reduction of LBP was accompanied with a significant QoL improvement and reduction of pain impact on daily activities. The improvements of QoL were statistically significant for all 9 domains and pain interference with usual daily activities was significantly reduced compared to baseline values in all the categories at all the visits. By the end of the study the biggest improvements were seen in pain interference with mood, sleep and general activity, where BPI score decreased by 4.86, 4.69 and 4.88, respectively.

We must take into account that before enrolment almost two thirds of patients (61%) tried other means for relieving pain. As for pharmacological treatment patients were mostly treated with NSAID and opioids, bearing in mind that some patients used more than one treatment option. It is worthy to note that pre-study treatment options were not sufficiently efficacious, as the level of pain remained to be of moderate to severe intensity (according to the VAS threshold value). Therefore, the failure of previous therapy emphasizes the importance of the present study findings, namely that the combination of T/P resulted in clinically meaningful improvement of LBP in the majority of patients.

Rescue medication is an indirect and validated endpoint for analgesic studies, and is used in the case of breakthrough pain. In a survey of chronic non-malignant pain (mostly LBP), 74% of patients with opioid-controlled baseline pain reported breakthrough pain (30). Treatment with T/P demonstrated good efficacy, as the administration of the rescue medication decreased during the study. In addition, compliance was very high (88%). Besides reflecting favourable tolerability of the study drug, good compliance can probably be also attributable to the fact that LBP usually limits physical activity in a significant manner, causing patients to seek pain relief in order to regain normal functioning.

The results obtained in this study are in concordance with those reported for other pain models, especially for musculoskeletal pain. The trial in which the combination of T/P for subacute pain was evaluated by Perrot et al. (18), compared the efficacy and tolerability of tramadol alone (50 mg) and T/P combination (37.5 mg/325 mg) in subacute LBP, with treatment satisfaction after 10 days as the primary efficacy variable. Overall patient satisfaction included both efficacy and tolerability of the treatment, according to a 4-point verbal rating scale. Moreover, pain intensity and pain relief were also evaluated (on 100-mm VAS) during the final study visit. Pain intensity which was comparable in both treatment groups (67.5 (13.0) in T/P group and 65.3 (14.6) in tramadol-only group) declined to mean pain intensity levels of 27.9 mm in T/P group and 24.8 mm in tramadol-only group till study end. In our study, the final evaluation of pain intensity revealed an even greater reduction of mean pain intensity, i.e. from 70.3 mm to 16.3 (19.6) mm.

Drug safety is one of the essential points in decision which drug to choose for treating a patient. In this study, safety criteria for evaluation were the incidence of ARs, stratified by specific type, with a special interest in the four main and most commonly reported ARs for tramadol (nausea, dizziness, vomiting, and constipation). By far most of the ARs in this study were mild; there was only 1 severe AR. The latter represents one of the 2 withdrawals that appeared in the study; additional withdrawal was due to moderate AR. Both withdrawals occurred in the 1st period of the study, inferring that majority of the withdrawals due to ARs are to be expected in early treatment. There was no serious adverse events in this study. This is in line with other studies where adverse event-related withdrawals occurred in < 1% of patients receiving single-dose T/P and in 5.2–28.1% of patients receiving multiple-dose T/P (during ≤ 2 years of treatment) (16). Most commonly reported ARs were nausea, dizziness, constipation, somnolence and vomiting - in this decreasing order of frequency occurrence. The highest proportion of these was declared in the 1st period of the study and decreased throughout the study, following with the 2nd period and 3rd period with the smallest proportion of patients. Also nausea, which was experienced by the biggest proportion of patients in the 1st period, was observed in last period only in 4 patients. In other clinical trials, where the most common (incidence > 6%) treatment-related - or probably or very likely treatment-related AEs upon T/P therapy for up to 3 months - were nausea (9–34.1%), dizziness (10.2–20.0%), vomiting (6.0–15.6%), somnolence (6.4–11.9%), and constipation (10.2%) (16). Percentages seen in the present study are within the range of these previously observed ones. Overall, the expected range of AEs as well as the low incidence of severe AEs, are important from the clinical point of view. The option of having both an efficacious drug with an acceptable safety profile of T/P

combination is a clear advantage and reassuring in the setting of a very prevalent condition such as aLBP.

The main strengths of this study are homogeneous population, carefully selected, commonly used and validated assessment tools, pre-defined response criteria, multiple measurements, additional emphasis on QoL and measuring the interference of pain with the QoL. The obvious weakness is lack of the placebo arm.

In conclusion, this 4-week study in patients with aLBP confirmed the efficacy of the immediate release T/P single pill combination on the level of pain intensity, the change in quality of life scales, and the change in the components of pain interference score. Also good compliance, on top of frequency and severity of treatment-related AEs, demonstrated good tolerability and safety of this combination. The data obtained in this study are also consistent with those reported for other pain conditions.

Acknowledgements: TREASURE trialist group: from Slovenia: Urška Herlah, Nada Hiti, Rade Iljaž, Primož Kuhar, Branko Jerkovič, Alenka Nadler Žagar, Mateja Plut Švigelj, Martina Horžen, Tatjana Kitić Jaklič, Barbara Prosen Udir, Aleksander Stepanovič, Zvezdica Rajnar Vöröš, Andreja Švajgelj, Nikolaj Benedičič, Vojislav Ivetić, Köveš Dean, Martina Hrovat, Martina Demšar; from Croatia: Tomislav Nemčić, Dijana Bešić, Martina Peloza, Dubravka Blažeković Čižmešija, Ksenija Kranjčević, Vera Hušman Miletić, Ana-Marija Sorić, Miljenko Kuljiš, Vjekoslava Amerl Šakić, Valerija Bralić-Lang; from Czech Republic: Šárka Koumarová, Marek Hakl; from Poland: Agnieszka Sękowska, Hanna Kucia, Maroun Chahwan, Anatol Mickielewicz, Elżbieta Choroszy-Grzesiak, Magdalena Szuflińska-Sidorowicz, Krystyna Gospodarczyk-Szot, Włodzimierz Frasunkiewicz, Jan Bembenek, Maciej Mierzejewski.

Source of funding: This study was sponsored by KRKA, d. d., Novo mesto, Slovenia.

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