2 SYNOPSIS

Study No.	FLUPI – 7018	**Clinical phase**	IV
Study acronym	SUPREME	**Type of study**	therapeutic, confirmatory, active-/placebo-controlled, non-inferiority vs. active control, superiority vs. placebo
Project	Katadolon® S Long	**Indication**	chronic low back pain

Title of the Study

A multicentre, double-blind, randomized, active- and placebo-controlled clinical trial on the pain relieving effects of the modified-release formulation of flupirtine in patients suffering from moderate to severe chronic low back pain.

Rationale of the Study

Flupirtine modified-release (MR) formulation plays an important role in the management of acute and chronic musculoskeletal – especially low-back – pain (LBP) in Germany. However, so far no scientific evidence (especially no data from active or placebo controlled randomized trials) exists, supporting its efficacy observed in daily practice. Due to this lack of scientific evidence flupirtine has neither been implemented nor recommended in current treatment algorithms.

Co-ordinating Investigator

[redacted]

Project Development

[redacted]

Contract Research Organisation (CRO)

[redacted]

Investigational Drug

Flupirtine modified-release 400mg tablets (Katadolon® S long), Batch No. 9B629

Active Comparator

Tramadol extended-release 200mg capsule (T-long® 200mg), Batch No. 9C007

Study Design

Double-blind, randomized, active- (comparative) and placebo-controlled, multicentre, parallel group, non-inferiority vs. active comparator, superiority vs. placebo;

Annotation: this study followed a "flare-design", in which patients were deemed eligible to participate if they experienced an appropriate exacerbation of their clinical symptomatology within 4-7 days after discontinuation of their current LBP therapies.

Study centres

31 centres in Germany (in alphabetical order):

[redacted]

Study period

Autumn 2009 – Spring 2011 (FPI: September 21, 2009; LPO: April 26, 2011)

Duration of treatment per subject

28 (±2) days [study duration per subject: 42 (±2) days]

Objectives

The primary objectives of this study were to demonstrate either non-inferior pain relieving effects of the modified-release formulation of flupirtine (400mg OD in the evening) in comparison to extended-release tramadol (200mg OD in the evening) as well as a superior analgesic efficacy of flupirtine MR (400mg OD in the evening) in comparison to placebo in patients suffering from moderate to severe chronic low back pain (CLBP) after a four week treatment course.

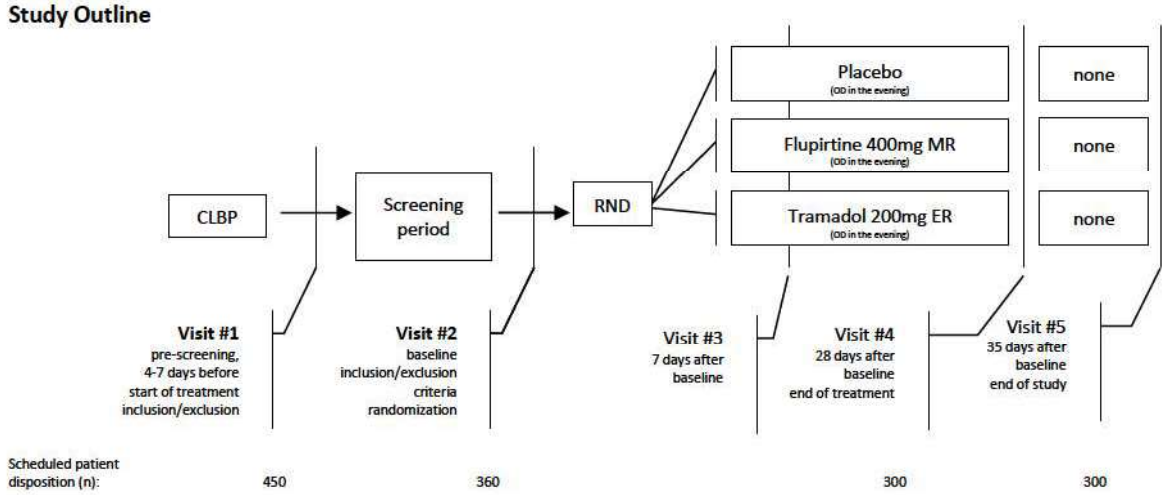
Secondary objectives focused on the differential impact of the treatment with flupirtine or tramadol on pain-related disabilities in daily life activities, on the health-related quality-of-life and the overall efficacy with respect to the different stages of chronification.

Safety and tolerability of both active comparators were descriptively evaluated based on adverse events, affected patients, vital signs and laboratory parameters.

Methodology

Prospective, double-blind, randomized, active- (comparative) and placebo-controlled, multicentre, parallel group study. After an initial screening phase of up to 7 days eligible patients with chronic low-back pain (12 weeks or longer) of moderate to severe intensity were randomly allocated to a 28 day treatment with either placebo, 400mg modified-release flupirtine or 200mg extended-release tramadol.

Study Outline



Study outline. CLBP: chronic low back pain; RND: randomization; MR: modified release; ER: extended release.

Inclusion criteria

- male or female patients, aged 18 to 75 (inclusive)
- chronic low back pain (>12 weeks)
- pretreatment with either NSAIDs, cox-2 inhibitors, dipyrone or paracetamol as recommended by national LBP treatment guidelines
- mild to moderate stage of pain chronification (stage I or II) according to the Mainz Pain Staging System *(MPSS).*
- an average pain intensity classified as moderate to severe at baseline (i.e. at least "4" on the NRS-11 or at least "moderate" on the VRS-5).
- significant worsening of pain intensity after discontinuation of the analgesic pre-study medication with a deterioration of both, the average low back pain intensity (of at least 1 point on the NRS-11 and one point on the VRS-5) and one point on the 5-point patient global assessment of response to therapy (PGART) scale
- women of childbearing potential must have used a reliable method of contraception
- patients must have given written informed consent, after having been informed about benefits and potential risks of the trial, as well as details of the insurance taken out to cover the subjects participating in the study.

Exclusion criteria

Lack of suitability for the trial

- a rating of the patient global assessment of disease status (PGADS) as very poor
- no significant worsening of the average low back pain intensity and PGART after discontinuation of the analgesic pre-study medication
- back pain caused by any spinal fracture (e.g. osteoporotic crush).
- history of any surgery in the back.
- clinical and radiological evidence of Bechterew's or Paget's disease.
- clinical signs for acute nerve root lesion (hyporeflexia, weakness, dermatomal sensory deficite).
- acute back pain caused by soft tissue damage.
- malignant diseases with involvement of the spinal column.
- metabolic bone diseases.
- chronic inflammatory diseases of the spinal column due to Psoriasis arthritis, Reiter syndrome, arthritides in connection with enteropathies (Colitis ulcerosa, M. Crohn).
- necessity for simultaneous administration of not permitted medication during the study (incl. topical preparations applied to the pain area, local injections).
- necessity of other concomitant, pain relieving therapy measures during the study.
- concomitant disease: clinically significant abnormalities on pre-examination, vital signs, or laboratory tests.
- pain-free states during daytime during the screening period (as stated in the patient diary).
- tailored treatment targets of "0" or "1" (NRS-11) at screening visit.
- hepatic impairment and increased liver enzymes (GOT, GPT and GGT, ↑ twice the upper reference range).
- neurological or psychiatric disease or drug or alcohol abuse which would have interfered with the subjects proper completion of the study.

Safety concerns

- history of allergic reaction to flupirtine, tramadol, diclofenac or to excipients of their pharmaceutical preparations.
- contraindications to flupirtine, tramadol or diclofenac
- lactating female or female of child-bearing potential not employing adequate contraception.

Administrative reasons

- lack of ability or willingness to give informed consent.
- patients who were unable to co-operate.
- anticipated non-availability for study visits/procedures.
- exposure to another investigational agent within the last 30 days.

Study medication, dose and mode of administration

	Mode of administration	Group 1	Group 2	Group 3
Double blind treatment phase, 4 weeks	tablets (flupirtine MR 400mg) or capsules (tramadol ER 200mg) or matching placebo once daily in the evening	1 x 400 mg flupirtine MR 1 x placebo capsule matching tramadol	1 x 200 mg tramadol ER 1 x placebo tablet matching flupirtine	1 x placebo tablet matching flupirtine 1 x placebo capsule matching tramadol

Rescue medication

Diclofenac tablets (50mg/dose)

Criteria for evaluation (efficacy and safety)

Efficacy

Primary

a) the change in the low-back pain intensity index (LBPI) between treatment visit 4 (day 29, week 4) and baseline (visit 2) was the primary endpoint of this study.

Secondary

b) percentage of patients with a meaningful/perceivable reduction in their LBPI (defined as a 50%/30% relief between baseline (visit 2), day 8 (visit 3) and day 29 (visit 4).
c) change in LBPI between baseline (visit 2) and day 8 (visit 3)
d) degree of pain relief (VRS-5) at day 8 (visit 3) and day 29 (visit 4) .
e) change in pain-related disability (as assessed by the modified pain-related disability index) between baseline (visit 2) and day 29 (visit 4).
f) change in low back pain bothersomeness scale (LBP-BS, VRS-5) at day 29 (visit 4) in comparison to baseline (visit 2).
g) change in quality-of-life as assessed by SF-12 at day 29 (visit 4) in comparison to baseline (visit 2), and as assessed by QLIP.
h) change in patient/investigator global assessment of response to therapy (PGART/IGART) between baseline (visit 2) and day 29 (visit 4).
i) global assessment of efficacy as assessed by a 7-point Patient Global Impression of Change Scale (PGIC) at day 29 (visit 4).
j) proportion of patients reaching their tailored treatment target (TTT) at day 8 (visit 3) and day 29 (visit 4).
k) use of rescue medication.

Safety

l) adverse events (AEs)
m) safety parameters (blood pressure, pulse rate, laboratory, global assessment of tolerability)

Statistical methods:

Stratification

During this trial no a-priori stratification has been performed.

Randomization and block size

Randomization followed a computer generated allocation list with a block-size of 6 and a 1:1:1 ratio.

Efficacy data:

Primary:

This study followed a combined non-inferiority/superiority design and compared the analgesic efficacy of the modified-release formulation of flupirtine to those of the extended-release formulation of tramadol (non-inferiority) and to placebo (superiority). The change in the low back pain intensity index after a four week treatment course with either modified-release flupirtine, extended-release tramadol or placebo was analyzed as primary endpoint using an adjusted analysis of covariance (ANCOVA) model including disease duration and pre-study analgesic medication as terms and the baseline LBPI as a covariate.

Due to balanced characteristics across treatment arms, there was no need for further baseline parameters to be taken into account as covariates to adjust for any imbalances and/or potential confounders that occur despite randomization.

The alternative (working) hypotheses were ...

a) ... that the analgesic efficacy of modified-release flupirtine (400mg OD) in chronic low back pain patients is over a four week treatment course superior to placebo;

b) ... that the analgesic efficacy of modified-release flupirtine (400mg) in chronic low back pain patients is over a four week treatment course comparable (i.e. non-inferior) to extended-release tramadol (200mg OD).

Annotation: this hypothesis was defined to be confirmed, if the 95% confidence interval for the difference in pain intensity lies entirely above the specified non-inferiority limit of "-1").

Secondary:

As for the primary analysis, an adjusted analysis of covariance (ANCOVA) model has been used to assess the time-specific response in case of continuous quantitative outcome variables. In case of ordered qualitative or binary outcome variables a logistic regression model and in case of time-specific outcome events a Cox regression model has been used. In addition to the time-specific analyses, time-weighted average procedures have been performed for all (primary and secondary) efficacy parameters derived from post baseline measurements if appropriate to obtain some information on the time-course of the observed treatment effects.

Safety data

Safety and tolerability data have been assessed by statistical and clinical review of adverse events, discontinuations due to adverse events, laboratory values and vital signs. All patients who received at least one dose of study medication have been included in this safety and tolerability analyses. Primary variable for the safety assessment was the incidence of clinical adverse events that occurred after the start of this trial and within 30 days after its completion.

Interim analysis

No interim analysis has been performed.

Flow chart

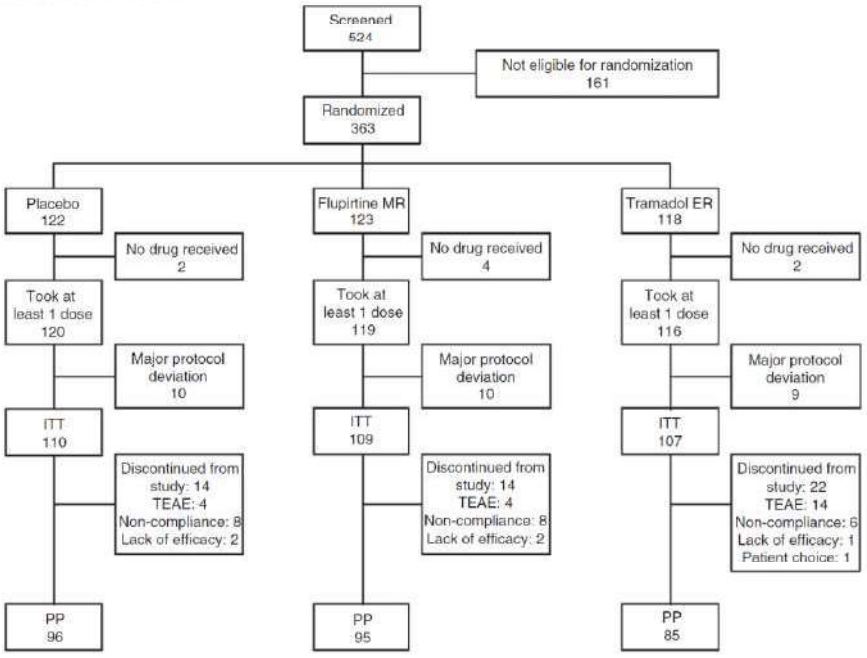
Visit	1 screening	2 baseline start of treatment	3	interim phone interview	4 end of treatment	5 final end of study
Time – Day	-7	1	8 (±2)	15 (±2)	29 (±2)	36 (±2)
Medication						
Flupirtine MR 400 mg/d or tramadol ER 200mg/d or placebo;		x	x		x	
General activities						
Informed consent	x					
Demography / medical history	x					
Concomitant diseases	x					
Concomitant medication	x	x	x		x	x
Previous analgesic medication	x	x				
In-/exclusion criteria	x	x				
Safety laboratory	x				x	
Physical examination	x	x			x	
Blood pressure and pulse rate	x	x	x		x	x
Withdrawal of not permitted medication	x					
Randomization		x				
Dispense of study medication		x	x			
Drug accountability			x		x	
Return of study medication			x		x	
Dispense of patient diary	x	x	x		x	
Return of patient diary		x	x		x	x
Adverse events		x	x	x	x	x
Dispense of rescue medication (diclofenac)	x	x	x		x	
Use of rescue medication (diclofenac)		x	x		x	x
Return of rescue medication		x	x		x	x
Status fax	x	x	x		x	x
Pain relevant assessments						
Mainz pain staging system (MPSS)	x					
Patient global assessment of disease status (PGADS)	x	x	x		x	x
Patient global assessment of response to therapy (PGART)	x	x	x		x	x
Low back pain bothersomeness scale (LBP-BS)	x	x	x		x	x

Flow chart (contd.)

Visit	1 screening	2 baseline start of treatment	3	interim phone interview	4 end of treatment	5 final end of study
Time – Day	-7	1	8 (±2)	15 (±2)	29 (±2)	36 (±2)
Pain relevant assessments (contd.)						
Pain intensity (PI)	x	x	x	x	x	x
Tailored treatment target (TTT)	x					
Modified Pain Disability Index (mPDI-7; diary)		x			x	
Health-related quality-of-life (QLIP; diary)		x	x	x	x	x
Health-related quality-of-life (SF-12; diary)		x			x	
Patient global impression of change (PGIC)					x	
Patient global assessment of tolerability (PGAT)			x		x	
Investigator global assessment of response to therapy (IGART)	x	x	x		x	
Investigator global assessment of tolerability (IGAT)			x		x	
Investigator global impression of change (IGIC)					x	

Results

Number / disposition of patients



MR: modified release; ER: extended release; ITT: intent-to-treat; PP: per-protocol; TEAE: treatment emergent adverse event.

A total of 524 patients were screened, of whom 363 were eligible for randomization to placebo (n=122), flupirtine MR (n=123), or tramadol ER (n=118). Eight patients were lost to follow up without any post-baseline measure, resulting in a safety population of 355 patients (placebo: n=120, flupirtine MR: n=119, and tramadol ER: n=116).

Twenty-nine patients who were initially randomized despite the fact that they did not meet the inclusion criteria were excluded from the analysis as randomization failures prior to unblinding, resulting in an ITT population of 326 patients (placebo: n=110, flupirtine MR: n=109, tramadol ER: n=107) which met the predefined requirements of the sample size estimation (considering a statistical power of 90%).

The percentages of patients who completed the study in the placebo, flupirtine MR, and tramadol ER groups were 87.3% (96/110), 87.2% (95/109), and 79.4% (85/107), respectively. Primary reasons for treatment discontinuation in all three treatment groups were non-compliance (placebo: 8/110, 7.3%; flupirtine MR: 8/109; 7.3%; tramadol ER: 6/107, 5.6%) and treatment emergent adverse events especially for tramadol ER (placebo: 4/110, 3.6%; flupirtine MR: 4/109, 3.7%; tramadol ER: 14/107, 13.1%). Two subjects discontinued each from placebo and flupirtine MR and one from tramadol ER due to lack of efficacy, and one patient from the tramadol ER population withdrew consent, resulting in a per-protocol population of 276 patients.

Patient demographics

Demographic and baseline characteristics were similar between all three treatment groups. Overall, treatment groups were well balanced with regard to their demographic and baseline characteristics.

	Overall (n=355)	Placebo (n=120)	Flupirtine MR (n=119)	Tramadol ER (n=116)
Age, years; mean (SD)	58.5 (12.1)	59.2 (10.7)	58.6 (13.0)	57.6 (12.4)
Age ≥65 years; n (%)	138 (38.9)	45 (37.5)	51 (42.9)	42 (36.2)
Race: white; n (%)	351 (98.9)	118 (98.3)	119 (100.0)	114 (95.8)
black; n (%)	4 (1.1)	2 (1.7)	- -	2 (4.2)
Gender female; n (%)	220 (62.0)	67 (55.8)	82 (68.9)	71 (61.2)
Body mass index, kg/m^2; mean (SD)	29.7 (6.1)	29.5 (5.8)	29.9 (6.2)	29.8 (6.4)
Systolic blood pressure, mmHG; mean (SD)	134.2 (15.0)	135.4 (15.9)	132.2 (14.9)	135.1 (14.0)
Diastolic blood pressure, mmHG; mean (SD)	81.4 (9.8)	81.3 (9.5)	81.3 (8.6)	81.6 (11.1)
Heart Rate; mean (SD)	71.4 (9.2)	70.9 (9.8)	71.0 (8.6)	72.4 (9.0)
Comorbidities: cardio-vascular system; n (%)	170 (47.9)	55 (45.8)	54 (45.4)	61 (52.6)
Pulmonary tract; n (%)	29 (8.2)	10 (8.3)	6 (5.0)	13 (11.2)
Hepato-/gastrointestinal system; n (%)	71 (20.0)	26 (21.7)	24 (20.2)	21 (18.1)
Renal/urogenital system: n (%)	50 (14.1)	13 (10.8)	16 (13.4)	21 (18.1)
Metabolism/endocinology; n (%)	128 (36.1)	45 (37.5)	45 (37.8)	38 (32.8)
Hematology; n (%)	17 (4.8)	5 (4.2)	4 (3.4)	8 (6.9)
Immune system/allergies; n (%)	55 (15.5)	16 (13.3)	21 (17.5)	18 (15.5)
Nervous system; n (%)	36 (10.1)	12 (10.0)	11 (9.2)	13 (11.2)
Psychiatric disorders; n (%)	28 (7.9)	6 (5.0)	10 (8.4)	12 (10.3)
Sense organs; n (%)	37 (10.4)	14 (11.7)	11 (9.2)	12 (10.3)
Skin; n (%)	31 (8.7)	8 (6.7)	14 (11.8)	9 (7.8)
Others; n (%)	97 (27.3)	31 (25.8)	28 (23.5)	38 (32.8)
PGADS "≤fair"; n (%)	211 (59.4)	73 (60.8)	69 (58.0)	69 (59.5)

Patient demographic and baseline characteristics (safety population)

MR: modified release; ER: extended release; SD: standard deviation; PGADS: patient global assessment of disease.

Efficacy

Least square (LS) mean±SD changes of the low back pain intensity index (LBPIX) from baseline at week 4 were clinically significant for all three treatment groups of the modified intent-to-treat (ITT) and the per-protocol (PP) population: placebo: -1.81±1.65/-1.77±1.59, flupirtine MR: -2.23±1.73/-2.28±1.68, and tramadol ER: -1.92±1.84/2.03±1.83 (p<0.001 for each).

Significantly more ITT patients treated with flupirtine MR (59.6/37.6%) showed a ≥30/50% relief of the low back pain intensity index in comparison to placebo (46.4/24.6%; significance vs. flupirtine MR: p=0.049/0.037). ITT treatment contrasts for tramadol (46.7/26.2%) failed to reach significance vs. placebo.

Intent-to-Treat Population (n=326)	Placebo (n=110)	Flupirtin MR (n=109)	Tramadol ER (n=107)	Significance F vs. P	T vs. P	F vs. T
LBP intensity index (LBPIX); NRS_{11}						
Baseline (V2); mean (SD)	5.94 (1.44)	5.72 (1.25)	5.85 (1.21)	ns	ns	ns
Week 4 (V4); mean (SD)	4.13 (1.99)	3.49 (1.79)	3.93 (1.92)	0.013	ns	ns
Difference V4→V2; mean (SD)	-1.81 (1.65)	-2.23 (1.73)	-1.92 (1.84)	0.003	ns	ns
Significance V4→V2	<0.001	<0.001	<0.001			
response ≥30%	51 (46.4)	65 (59.6)	50 (46.7)	0.049	ns	ns
≥50%	27 (24.6)	41 (37.6)	28 (26.2)	0.037	ns	ns
≥3 NRS_{11}	33 (30.0)	47 (43.1)	33 (30.8)	0.044	ns	ns
≥TTT	31 (28.2)	45 (41.3)	32 (29.9)	0.042	ns	ns

Per-Protocol Population (n=276)	Placebo (n=96)	Flupirtin MR (n=95)	Tramadol ER (n=85)	Significance F vs. P	T vs. P	F vs. T
LBP intensity index (LBPIX); NRS_{11}						
Baseline (V2); mean (SD)	5.81 (1.38)	5.68 (1.13)	5.91 (1.25)	ns	ns	ns
Week 4 (V4); mean (SD)	4.04 (1.94)	3.40 (1.69)	3.88 (1.82)	0.016	ns	ns
Difference V4→V2; mean (SD)	-1.77 (1.59)	-2.28 (1.68)	-2.03 (1.83)	0.033	ns	ns
Significance V4→V2	<0.001	<0.001	<0.001			
response ≥30%	44 (45.8)	56 (59.0)	40 (47.1)	ns	ns	ns
≥50%	25 (26.0)	34 (35.8)	24 (28.2)	0.047	ns	ns
≥3 NRS_{11}	26 (27.1)	31 (32.6)	22 (25.9)	ns	ns	ns
≥TTT	23 (24.0)	30 (30.5)	21 (24.7)	ns	ns	ns

Treatment-related changes of the low back pain intensity index (LBPIX) for the modified intent-to-treat and the per-protocol population.

MR: modified release; ER: extended release; P: placebo; F: flupirtine MR; T: tramadol ER; LBPIX: low back pain intensity index; NRS_{11}: 11-point numerical pain intensity rating scale (0=no pain, 10=worst pain conceivable); SD: standard deviation

Flupirtine MR reached both primary efficacy endpoints: ITT/PP treatment effects for flupirtine MR (-2.23/-2.28) were non-inferior when compared with tramadol ER (-1.92/-2.03) and superior when compared with placebo (-1.81/-1.77; p=0.003/0.033).

Population (n)	Study group (n)	LBPIX difference V4→V2 mean	(SD)	95% CI	Treatment contrast F vs. P mean	95% CI	Sign.	Treatment contrast T vs. P mean	95% CI	Sign.	Treatment contrast F vs. T mean	95% CI	Sign.
ITT (326)	Placebo (110)	-1.81	1.65	-1.96 / -1.65									
	Flupirtine MR (109)	-2.23	1.73	-2.39 / -2.07	-0.42	-0.76 / -0.09	p=0.003	-0.11	-0.24 / 0.48	ns	-0.31	-0.69 / 0.09	ns
	Tramadol ER (107)	-1.92	1.84	-2.10 / -1.75									
PP (276)	Placebo (96)	-1.77	1.59	-2.01 / -1.66									
	Flupirtine MR (95)	-2.28	1.68	-2.62 / -2.04	-0.51	-0.98 / -0.04	p=0.033	-0.26	-0.77 / 0.26	ns	-0.25	-0.75 / 0.25	ns
	Tramadol ER (85)	-2.03	1.83	-2.42 / -1.63									

Primary endpoint at week 4 (modified intent-to-treat and per-protocol population)

MR: modified release; ER: extended release; P: placebo; F: flupirtine MR; T: tramadol ER; LBPIX: low back pain intensity index; V2=baseline; V4=end of treatment (week 4); SD: standard deviation; ITT: intent-to-treat; PP: per-protocol

Safety

Within the safety population, flupirtine MR was associated with a significantly lower incidence of treatment-emergent adverse events (TEAEs; 21.0%) and TEAE-related study discontinuations (3.4%) than tramadol ER (34.5/12.0%; p=0.039/0.017) and exhibited an overall safety/tolerability profile non-inferior to placebo (15.8/3.3%; p=ns for each). Routinely performed laboratory analyses detected 12 patients with at least one laboratory parameter suspicious for liver toxicity (6 in the flupirtine MR, 5 in the placebo and 1 in the tramadol ER group), however without any clinical correlates. With an 0.8% difference in prevalence rates between flupirtine MR and placebo, the raw risk of a patient to develop a flupirtine-related increase in liver enzymes corresponds – according to the usual classification system – to those of uncommon events (i.e. ≥1/1,000 to <1/100).

Study limitations

Major limitations of this study were the short treatment duration, the comparison of different drug classes and the lack of a titration phase.