Scandinavian Journal of Pain 17 (2017) 134–143

Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Clinical pain research

A randomized study to evaluate the analgesic efficacy of a single dose of the TRPV1 antagonist mavatrep in patients with osteoarthritis

Arthur J. Mayorga[a,*], Christopher M. Flores[a], Jeremiah J. Trudeau[a], John A. Moyer[a], Kevin Shalayda[a], Mark Dale[b], Mary Ellen Frustaci[a], Nathaniel Katz[c,d], Prasarn Manitpisitkul[a], Roi Treister[c,d,e], Stuart Ratcliffe[f], Gary Romano[a]

[a] *Janssen Research & Development, LLC, Titusville, NJ, USA*
[b] *MAC Clinical Research, Manchester, UK*
[c] *Analgesic Solutions, Natick, MA, USA*
[d] *Tufts University School of Medicine, Boston, MA, USA*
[e] *Massachusetts General Hospital & Harvard Medical School, Department of Neurology, Nerve Injury Unit, Boston, MA, USA*
[f] *St Pancras Clinical Research, London, UK*

HIGHLIGHTS

- First report of analgesic effect of a TRPV1 antagonist in a chronic pain condition.
- Stair-climbing-pain model improved discrimination of active drug from placebo.
- Mavatrep 50 mg was more efficacious for pain reduction than naproxen 500 mg.
- Mavatrep improved WOMAC pain, stiffness, and function at 7 days after a single dose.
- The safety profile of mavatrep was consistent with its mechanism (TRPV1 antagonist).

ARTICLE INFO

Article history:
Received 17 January 2017
Received in revised form 13 July 2017
Accepted 25 July 2017
Available online 24 August 2017

Keywords:
Efficacy
Knee osteoarthritis
Mavatrep
Pain
Safety
Randomized study

ABSTRACT

Background/Aims: Transient receptor potential vanilloid type 1 (TRPV1) receptor antagonists have been evaluated in clinical studies for their analgesic effects. Mavatrep, a potent, selective, competitive TRPV1 receptor antagonist has demonstrated pharmacodynamic effects consistent with target engagement at the TRPV1 receptor in a previous single-dose clinical study. The current study was conducted to evaluate the analgesic effects of a single dose of mavatrep.

Methods: In this randomized, placebo- and active-controlled, 3-way crossover, phase 1b study, patients with painful knee osteoarthritis were treated with a single-dose of 50 mg mavatrep, 500 mg naproxen twice-daily, and placebo. Patients were randomized to 1 of 6 treatment sequences. Each treatment sequence included three treatment periods of 7 days duration with a 7 day washout between each treatment period. The primary efficacy evaluation was pain reduction measured by the 4-h postdose sum of pain intensity difference (SPID) based on the 11-point (0–10) Numerical Rating Scale (NRS) for pain after stair-climbing (PASC). The secondary efficacy evaluations included 11-point (0–10) NRS pain scores entered into the Actiwatch between clinic visits, the Western Ontario and McMaster Universities Arthritis Index subscales (WOMAC) questionnaire, and use of rescue medication. Safety and tolerability of single oral dose mavatrep were also assessed.

Results: Of 33 patients randomized, 32 completed the study. A statistically significantly ($p < 0.1$) greater reduction in PASC was observed for mavatrep versus placebo (4-h SPID least square mean [LSM] [SE] difference: 1.5 [0.53]; $p = 0.005$ and 2-h LSM [SE] difference of PID: 0.7 [0.30]; $p = 0.029$). The mean average daily current pain NRS scores were lower in the mavatrep and naproxen treatment arm than in the placebo arm (mavatrep: 7 day mean [SD], 3.72 [1.851]; naproxen: 7 day mean [SD], 3.49 [1.544]; placebo: 7 day mean [SD], 4.9 [1.413]). Mavatrep showed statistically significant improvements as compared with placebo on the WOMAC subscales (pain on days 2 [$p = 0.049$] and 7 [$p = 0.041$], stiffness on day 7 [$p = 0.075$]), and function on day 7

DOI of refers to article: http://dx.doi.org/10.1016/j.sjpain.2017.08.015.
* Corresponding author at: Neuroscience Department, Janssen Research & Development, LLC, Titusville, NJ 08560, USA.
E-mail address: AMayorga@its.jnj.com (A.J. Mayorga).

http://dx.doi.org/10.1016/j.sjpain.2017.07.021

[$p = 0.077$]). The same pattern of improvement was evident for naproxen versus placebo. The mean (SD) number of rescue medication tablets taken during the 7-day treatment period was 4.2 (6.49) for mavatrep treatment, 2.8 (5.42) for naproxen, and 6.3 (8.25) for placebo treatment. All patients that received mavatrep reported at least 1 treatment emergent adverse event (TEAE). Feeling cold (79%), thermohypoesthesia (61%), dysgeusia (58%), paraesthesia (36%), and feeling hot (15%) were the most common TEAEs in the mavatrep group. Total 9% patients receiving mavatrep experienced minor thermal burns. No deaths or serious AEs or discontinuations due to AEs occurred.

Conclusion: Overall, mavatrep was associated with a significant reduction in pain, stiffness, and physical function when compared with placebo in patients with knee osteoarthritis. Mavatrep's safety profile was consistent with its mechanism of action as a TRPV1 antagonist.

Implications: Further studies are required to evaluate whether lower multiple doses of mavatrep can produce analgesic efficacy while minimizing adverse events, as well as the potential for improved patient counselling techniques to reduce the minor thermal burns related to decreased heat perception.

Trial Registration: 2009-010961-21 (EudraCT Number).

1. Introduction

Symptomatic knee osteoarthritis (OA) occurs in 10% men and 13% women and can affect younger individuals [1]. Pain relief in OA is mostly achieved with nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics or intra-articular corticosteroid injections. However, various limitations including limited efficacy, and adverse effects including peptic ulceration, substance abuse and noncompliance with these established treatment options, encourage discovery of newer drug options for OA pain [2–4].

Transient receptor potential vanilloid type 1 (TRPV1) is a calcium-permeable ion channel expressed in the central nervous system including all sensory ganglia and certain regions of the brain [5]. Upregulation of TRPV1 receptors in OA animal models and evidence from experiments with TRPV1 mutant mice and TRPV1 antagonists support the important role of TRPV1 receptor in pain and inflammatory sensory sensitization [6–11]. TRPV1 receptor agonists and antagonists have been evaluated in clinical studies [12,13] for their analgesic effects. One published report of a TRPV1 antagonist in OA of the knee failed to demonstrate efficacy [14].

Mavatrep is a potent, selective, competitive antagonist of the TRPV1 receptor with proven antihyperalgesic effects after oral administration in several rodent models of inflammatory pain [5]. Mavatrep dose- and time-dependently reversed carrageenan-induced thermal hyperalgesia. In a postsurgical model of pain in rats, mavatrep (30 mg/kg; p.o.) completely reversed incision-induced thermal hyperalgesia, with effects observed for up to 5 h after administration. The effects on thermal parameters such as the heat pain threshold that have been observed with mavatrep in the clinic were consistent with the preclinical profile of the compound.

Like other reported TRPV1 antagonists, including A-425619 [9,15], A-840257 [3], capsazepine [16], and BCTC [17], mavatrep (data not shown) exhibited little or no efficacy in reversing non-heat hypersensitivity associated with other models of pain, including mechanical pressure hypersensitivity associated with inflammation, tactile and cold hypersensitivity associated with neuropathy/nerve injury and acute responses to viscerochemical stimulation [18,19].

The primary objective of this study was to evaluate the pain reduction by a single dose of mavatrep, compared to placebo, as measured by the 4-h postdose Sum of Pain. Intensity Difference (SPID) based on the 11-point (0–10) Numerical Rating Scale (NRS) for pain following stair-climbing. Secondary objectives were to assess the safety and tolerability of single dose mavatrep; and its effect on pain at rest, post-stair-climbing pain, change in post-exercise pain, joint stiffness, and physical function compared to placebo or naproxen in patients with painful knee OA. Utility of a variety of advanced methods designed to improve the efficiency of clinical trials was also explored. A single dose of mavatrep was chosen to compare to 7 days of naproxen treatment based on mavatrep's long pharmacokinetic half-life [20]. Two mechanism-related safety issues have been encountered in the clinical development of TRPV1 antagonists: elevation in core body temperature [21] accompanying subjective feelings of body temperature change, and a decrease in thermal heat perception. Given that this effect could predispose exposed patients to the risk of thermal burns, patients were extensively counselled on this potential phenomenon during the screening process (see Methods). The current study included efficacy measures to assess the benefit of mavatrep in OA in light of this safety profile.

2. Methods

2.1. Study participants

Patients of either sex, aged 21–65 years (inclusive), with a primary diagnosis of Functional Class I-III OA of the knee, and meeting the American College of Rheumatology criteria for clinical classification of OA of the knee, were included in the study. Patients were to have had some degree of OA knee pain for 3 months (an average of at least 5 days per week) prior to screening and taking a non-opioid analgesic with benefit (prior use of opioids was acceptable provided they had not been used in the 2 weeks prior to screening). Patients routinely exposed to situations in which they could sustain thermal burns or who failed to appropriately complete a burn prevention measures training quiz were excluded from the study. The burn prevention measures training quiz was used to counsel subjects on the potential for loss of noxious heat perception and ensure their understanding of these precautions. In addition to the other inclusion/exclusion criteria, patients were selected for randomization using focused analgesia selection test (FAST), [10] a method to measure patients' pain reporting skills (Analgesic Solutions, Natick, MA, USA) and assessment of post stair-climbing procedure pain using a modified patient global impression of change (PGIC).

The FAST procedure included psychophysical sensory assessment and a battery of patient-reported outcome (PRO) instruments assessing various psychological constructs (e.g. fear of pain) [22]. During the FAST psychophysical assessment, a set of 49 noxious thermal stimuli, 7 exposures each of 7 temperatures ranging from 43 °C to 51 °C in randomize block-order, were applied to each patient's ventral forearm. Patients were asked to rate the pain intensity of each stimulus using a 100 mm Computerized Visual Analog Scale (CoVAS). These pain ratings were used to calculate metrics of pain reporting ability. FAST R^2 score was computed by

fitting intensity ratings to a non-linear regression model individualized for each patient based on their own scores. Deviations from the power function described by the model result in lower R^2 scores and represent poor pain reporting accuracy and/or consistency; e.g. a patient rating the intensity of 47 °C stimuli variously as 20 mm, 80 mm, 45 mm, etc. and reporting lower temperature stimuli as more painful than higher temperature trials. A patient who gave consistently similar ratings at each stimulus level with higher temperatures resulting in higher pain intensity would have a better fit to their model and higher FAST R^2 score. The FAST psychological battery included 5 PRO scores used for inclusions/exclusion: somatization, fear of pain, social desirability, anxiety, and hope for pain relief [10]. Patients with scores on the psychophysical assessment or psychological components that would place them in the bottom 10th percentile of any component score (based on previous data from OA patients) were excluded on the basis that their reports of pain intensity were more likely to be inaccurate or unreliable.

The stair-climbing procedure consisted of walking up and down a set of 8 stairs two times. Patients were instructed to use their normal gait for completing this task, and were encouraged to complete the task despite increasing pain. To qualify for the study, patients described the change in pain in their target knee post stair-climbing and only the patients who had a minimum pain post-stair-climbing $\geq$4 on the 11-point current pain NRS and a Patient Global Impression of Change (PGIC) of 5 (minimally worse), 6 (much worse), or 7 (very much worse) at visit 2 were included in the study. For efficacy assessments during the study, patients were asked to rate their current pain on the 11-point NRS before and after stair-climbing.

2.2. Study design

This was a randomized, double-blind, placebo- and active-controlled, 3-way crossover, phase 1b study conducted from August 17, 2009 to May 21, 2010 at a single clinical site in Manchester, United Kingdom. The study consisted of a screening phase (2 visits), a double-blind treatment phase (4 visits and 7 telephone contacts), and a follow-up phase (1 telephone contact). The total duration of participation in the study for an individual patient, was approximately 9 weeks (Fig. 1).

A list of burn prevention measures was reviewed with the patients at screening visit 1 and prior to discharge on day1 of each treatment period to ensure awareness of potential changes in heat perception that could be experienced after study drug administration. Patients were quizzed to ensure their understanding of the burn prevention measures prior to enrollment. Only patients answering all 10 questions correctly were enrolled in the study (no patients failed screening due to this criterion).

At screening visit 1 (day −14 to day −9), patients were required to discontinue all analgesic/NSAID medication and were provided with paracetamol 500 mg as a rescue medication. Rescue medication up to a maximum of 2 g/day was permitted, but patients were encouraged to refrain from taking rescue medication unless absolutely needed. Patients were not permitted to take rescue medication in the 12 h prior to all in-clinic study visits and for the duration of each in-clinic study visit. Patients who took rescue medication within 12 h of the clinic visit were asked to return the next day for their visit. Patients were required to document the doses of study drug and rescue medication on diary cards. At screening visit 2 (day −9 to day −4, at least 5 days after NSAID discontinuation), final screening procedures were performed. A full psychological FAST battery (standardized and abbreviated psychological + psychophysical) was performed at screening visit 1 and an abbreviated FAST psychological battery + psychophysical at screening was performed at visit 2.

At visit 3 (day 1), the patients were randomly assigned to 1 of 6 treatment sequences based on a computer-generated randomization schedule prepared by or under the supervision of the sponsor before the study. The 6 sequences represented all possible treatment combinations of study drug administration (a–b–c,a–c–b,b–a–c,c–a–b,c–b–a,b–c–a). Based on this randomization code, the study drug was packaged and labelled for each patient. Each treatment sequence included three treatment periods of 7 days duration with a 7 day washout between each treatment period. The three treatments were: mavatrep 50 mg single dose (Treatment A), naproxen 500 mg twice a day (Treatment B), and placebo (Treatment C). Since the 50 mg dose of mavatrep was found to be pharmacodynamically active in a previous single ascending dose study [20], this dose was selected for the current study. Double-dummy blinding utilized placebo tablets matching mavatrep and placebo capsules matching encapsulated naproxen; matching placebo were used for both mavatrep and naproxen. The three treatments were administered as follows:

Treatment A: day 1, mavatrep 50 mg + placebo of naproxen in the morning, and placebo of naproxen in the evening; days 2–7, placebo of naproxen in the morning and evening.

Treatment B: day 1, naproxen 500 mg + placebo of mavatrep in the morning, and naproxen 500 mg in the evening; days 2–7, naproxen 500 mg in the morning and evening.

Treatment C: placebo of mavatrep + placebo for naproxen in the morning, and placebo of naproxen in the evening; days 2–7, placebo of naproxen in the morning and evening.

During these 3 treatment periods, the patients stayed in the unit on day 1 of each period for approximately 8 h for safety and efficacy evaluations, and then were discharged from the unit.

2.3. Concomitant medications

Analgesics other than the study drug or rescue medication were prohibited for the entire duration of the study. Based on the preclinical CYP450 profile of mavatrep, non-analgesic concomitant medications metabolized by CYP2C8, CYP2C9, CYP2C19, or CYP2D6 were prohibited, with the exception of proton pump inhibitors. Other non-analgesic concomitant medications were permitted and recorded.

2.4. Study evaluations

2.4.1. Efficacy assessments

Efficacy evaluations were performed while patients were at rest (pre stair-climbing) and after stair-climbing at predose (baseline) and 2-h and 4-h postdose during the in-clinic dosing visit for each treatment period. Pain intensity was assessed by the patients using an 11-point (0–10) numerical rating scale (NRS) score.

To account for differences in baseline pain intensity among patients, pain scores for each patient were converted into pain intensity difference (PID) scores by subtracting them from the pain score taken at the predose baseline of each treatment period (positive scores indicate reduction in pain). Two-hour and 4-h PID scores were then summed over the observation period, and the summed scores were termed sum of pain intensity difference (SPID). The 4-h postdose SPID score for pain following stair-climbing (pain after stair-climbing [PASC]) was the primary efficacy endpoint.

The secondary efficacy evaluations included 11-point (0–10) NRS pain scores entered into the Actiwatch™ after discharge on day 1 of each treatment period, the Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire and the

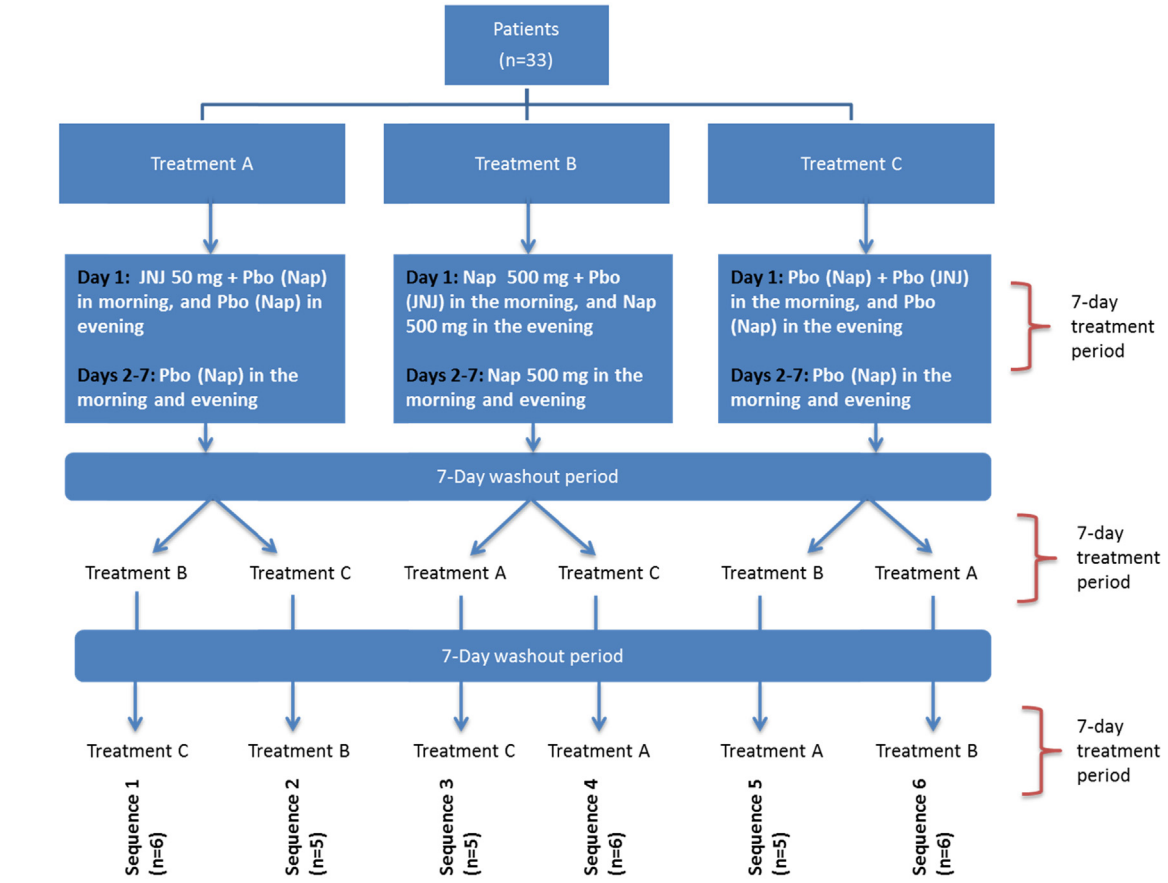

Fig. 1. Study design and patient disposition.

use of rescue medication. In between clinic visits, patients entered their daily current pain intensity NRS scores into Actiwatch™ device. The Actiwatch™ is a wrist-worn device that can be pre-programmed to alarm at specified time points (08:00, 12:00, 16:00, and 20:00) to prompt patients to enter a pain rating on the 11-point (0–10) NRS. The device also contains an accelerometer that has been used in a number of clinical trials to objectively measure levels of physical activity. On in-clinic days, Actiwatches were collected from patients in the morning and returned to them prior to discharge. In each treatment period, the WOMAC questionnaire was given prior to in-clinic study drug doses on day 1 and by telephone at days 2 and 7. The WOMAC™ 3.1 is a self-administered questionnaire containing 5 pain, 2 stiffness, and 17 physical function questions, responses to which are scaled on 5 point (none, mild, moderate, severe, extreme) scales resulting in subscale score sizes of 0–20 for pain, 0–8 for stiffness, 0–68 for physical function, and 0–96 for total score [23]. The version of the WOMAC questionnaire used for this study (LK 3.1) had a 24-h recall period, and has been validated for administration over the telephone [24]. Change from predose in WOMAC (total and subscales) at days 2 and 7 were analyzed.

2.4.2. *Pharmacokinetic assessments*

Blood samples were collected at approximately 6 h post morning dose on the first day of treatment and at the follow-up visit for the determination of mavatrep concentrations using a validated specific, and sensitive liquid chromatography–mass spectrometry (LC–MS/MS). Due to limited blood collections in this study, no formal pharmacokinetic analyses were performed.

2.4.3. *Safety assessments*

Safety assessments included evaluation of treatment-emergent adverse events (TEAEs), clinical laboratory parameters (i.e., haematology, serum chemistry, coagulation, and urinalysis measurements), electrocardiograms, vital signs, and physical examinations. Adverse events (AEs) of thermal burn were carefully assessed and documented.

2.4.4. *Statistical methods*

The analgesic effect size of a TRPV1 antagonist was unknown, therefore the sample size was based on the typical analgesic effect size of NSAIDS based on the authors' previous experience. In order to detect a difference between placebo and active treatments of 1.0 on the 11-point (0–10) pain NRS using a pre-specified alpha = 0.1, 2-sided, and assuming a standard deviation (SD) of 2.0, it was estimated that 27 patients would need to complete the study to have 80% power. It was estimated that 25% of patients would discontinue prematurely, and therefore approximately 36 patients were intended to be randomized to ensure completion of at least 27 patients. Efficacy analyses were performed for all patients completing at least two treatment periods. Statistical analyses using ANOVA modelling appropriate for a 3-way crossover design was performed to compare pairs of treatments with respect to the primary and secondary endpoints. Analyses of efficacy assessments were two-sided with a significance level of 0.1, as is appropriate for a signal-finding proof-of concept study. There was no adjustment for multiple comparisons. The baseline assessment value was used as a covariate; treatment, period, and sequence were used as fixed effects, and patients nested within sequence were used as a random effect. The point estimates and 90% confidence intervals

Table 1
Demographics and baseline characteristics.

	Total ($N = 33$)
Sex, *n* (%)	
Female	11 (33.3)
Male	22 (66.7)
Race, *n* (%)	
White	32 (97.0)
Others	1 (3.0)
Ethnicity, *n* (%)	
Not Hispanic or Latino	33 (100)
Age (years)	
Mean (SD)	52.3 (8.1)
Median	55.0
Baseline weight (kg)	
Mean (SD)	87.2 (14.9)
Median	88
Baseline height (cm)	
Mean (SD)	170.2 (8.5)
Median	171
Baseline BMI (kg/m^2)	
Mean (SD)	30.1 (4.6)
Median	29.3
Baseline temperature (°C)	
Mean (SD)	36.7 (0.2)
Median	36.7
Baseline pulse (bpm)	
Mean (SD)	68.1 (12.6)
Median	66.0

(CI) for the difference in least square means (LSM) for each comparison (mavatrep versus placebo, naproxen versus placebo, and mavatrep versus naproxen) were calculated. A separate statistical model based on the method suggested by Littell et al. [25] was used to assess carryover effects directly for all outcomes. The safety population comprised all patients who received at least one dose of any study drug, and safety parameters were summarized using descriptive statistics.

3. Results

3.1. Study participants

A total of 63 patients were screened, of which 33 were randomized. A total of 17 patients were excluded prior to randomization based on poor pain reporting accuracy on the FAST (11 on psychosocial parameters, 5 for psychophysical, 1 for both). Thirty-two randomized patients completed the study, and one patient was withdrawn from the study on day 15 due to concomitant use of gliclazide, a prohibited medication. All patients were included in the safety analysis population.

The majority of patients were men (66.7%) with a median (range) age of 55.0 (31–63) years and body mass index of 30.1 (4.6) kg/m^2. Most patients (97%) were white, and the baseline characteristics were comparable across groups (Table 1).

3.2. Efficacy results

3.2.1. Primary efficacy

3.2.1.1. 4-h postdose SPID – PASC. Mean (SD) 4-h postdose SPID PASC scores were 3.1 (2.79), 2.1 (2.66), and 1.2 (2.07), respectively for mavatrep, naproxen, and placebo. Based on the statistical model used, the LSM (SE) difference between mavatrep and placebo was statistically significant ($p = 0.005$) for 4-h SPID PASC, indicating a greater reduction in pain intensity in the mavatrep treatment group than in the placebo group. The LSM (SE) difference for 4-h SPID PASC was not significant between naproxen and placebo ($p = 0.229$) while it was significantly greater for mavatrep versus naproxen ($p = 0.088$) (Table 2).

3.2.2. Secondary efficacy

3.2.2.1. 4-h postdose SPID – pain at rest. Mean (SD) 4-h SPID scores at rest (before stair-climbing) were 1.9 (2.88), 1.9 (3.37), and 0.8 (2.21), respectively for mavatrep, naproxen, and placebo. Based on the statistical model, no statistically significant differences were observed for mavatrep versus placebo ($p = 0.220$), naproxen versus placebo ($p = 0.364$), or mavatrep versus naproxen ($p = 0.749$), confirming the greater sensitivity of the evoked pain measure (Table 2).

3.3. PID assessments

The 2-h and 4-h postdose PID results were consistent with the primary efficacy results. The 2-h postdose PID was of particular interest to better understand the onset of action of mavatrep. Mean (SD) 2-h PID scores after stair-climbing were 1.1 (1.55), 0.9 (1.31), and 0.3 (1.00), respectively for mavatrep, naproxen, and placebo. At rest, the respective scores were 0.7 (1.80), 0.8 (1.55), and 0.1 (1.01). Based on the statistical model, the 2-h PID score PASC for mavatrep was statistically significantly greater than that for placebo ($p = 0.029$). No other statistically significant differences between treatments were observed (Table 3).

3.4. Current pain – NRS Actiwatch™ assessments

Mean average daily current pain NRS scores were numerically lower in the mavatrep (7 day mean [SD], 3.72 [1.851]) and naproxen (7 day mean [SD], 3.49 [1.544]) treatment arms as compared with the placebo arm (7 day mean [SD], 4.9 [1.413]) over the 7-day treatment period. However, no statistically significant differences were observed for placebo versus mavatrep ($p = 0.288$), mavatrep versus naproxen ($p = 0.975$), or placebo versus naproxen ($p = 0.271$).

3.5. WOMAC questionnaire

Mavatrep and naproxen demonstrated improvement in WOMAC pain, stiffness, and physical function as compared with placebo (Fig. 2). Based on the statistical model, mavatrep showed statistically significant improvements as compared with placebo on the WOMAC subscales (pain on days 2 [$p = 0.049$] and 7 [$p = 0.041$], stiffness on day 7 [$p = 0.075$], and function on day 7 [$p = 0.077$]). The same pattern of improvement was evident for naproxen versus placebo (pain on days 2 [$p = 0.043$] and 7 [$p = 0.028$], stiffness on day 7 [$p = 0.066$], and function on day 7 [$p = 0.053$]). There were no statistically significant differences between mavatrep and naproxen.

3.6. Use of rescue medication

The mean (SD) number of rescue medication tablets taken during the 7-day treatment period was 4.2 (6.49) for mavatrep treatment, 2.8 (5.42) for naproxen, and 6.3 (8.25) for placebo treatment. Statistically significant differences were observed for mavatrep versus placebo ($p = 0.061$) and naproxen versus placebo ($p = 0.006$), but not for mavatrep versus naproxen ($p = 0.340$).

3.7. NRS responder analysis – in-clinic assessments

The percentage of patients who achieved a moderate treatment response (i.e., an improvement of ≥30% versus baseline) or a substantial improvement (i.e., an improvement of ≥50% versus baseline) on the NRS using in-clinic assessments are summarized in

Table 2
Analysis of 4-h postdose SPID following stair-climbing procedure and at rest (using 11-point NRS scale).

Reference group			Testing group			Testing-reference			
Treatment	*N*	LS mean	Treatment	*N*	LS mean	LS mean	SE	90% CI	*p*-value
SPID following stair-climbing procedure									
Placebo	32	1.4	Naproxen	32	2.0	0.6	0.53	(−0.24; 1.52)	0.229
Placebo	32	1.4	Mavatrep	33	2.9	1.5	0.53	(0.66; 2.43)	0.005
Naproxen	32	2	Mavatrep	33	2.9	0.9	0.52	(0.03; 1.78)	0.088
SPID at rest									
Placebo	32	1.1	Naproxen	32	1.6	0.5	0.57	(−0.44; 1.49)	0.364
Placebo	32	1.1	Mavatrep	33	1.8	0.7	0.57	(−0.25; 1.66)	0.220
Naproxen	32	1.6	Mavatrep	33	1.8	0.2	0.56	(−0.76; 1.12)	0.749

SPID calculated as sum of PID at 2-h and 4-h postdose on days 1/15/29.
CI: confidence interval; LS: least square; SE: standard error; NRS: numerical rating scale; SPID: sum of pain intensity difference.

Table 3
Analysis of 2-h postdose PID following exercise and at rest (using 11-point NRS scale).

Reference group			Testing group			Testing-reference			
Treatment	*N*	LS mean	Treatment	*N*	LS mean	LS mean	SE	90% CI	*p*-value
PID following stair-climbing procedure									
Placebo	32	0.4	Naproxen	32	0.8	0.5	0.30	(−0.01; 0.99)	0.108
Placebo	32	0.4	Mavatrep	33	1	0.7	0.30	(0.17; 1.17)	0.029
Naproxen	32	0.8	Mavatrep	33	1	0.2	0.30	(−0.31; 0.68)	0.539
PID at rest									
Placebo	32	0.3	Naproxen	32	0.6	0.3	0.31	(−0.17; 0.85)	0.268
Placebo	32	0.3	Mavatrep	33	0.6	0.3	0.30	(−0.20; 0.82)	0.310
Naproxen	32	0.6	Mavatrep	33	0.6	0	0	(−0.53; 0.47)	0.916

CI: confidence interval; LS: least square; NRS: numerical rating scale; SE: standard error; PID: pain intensity difference.

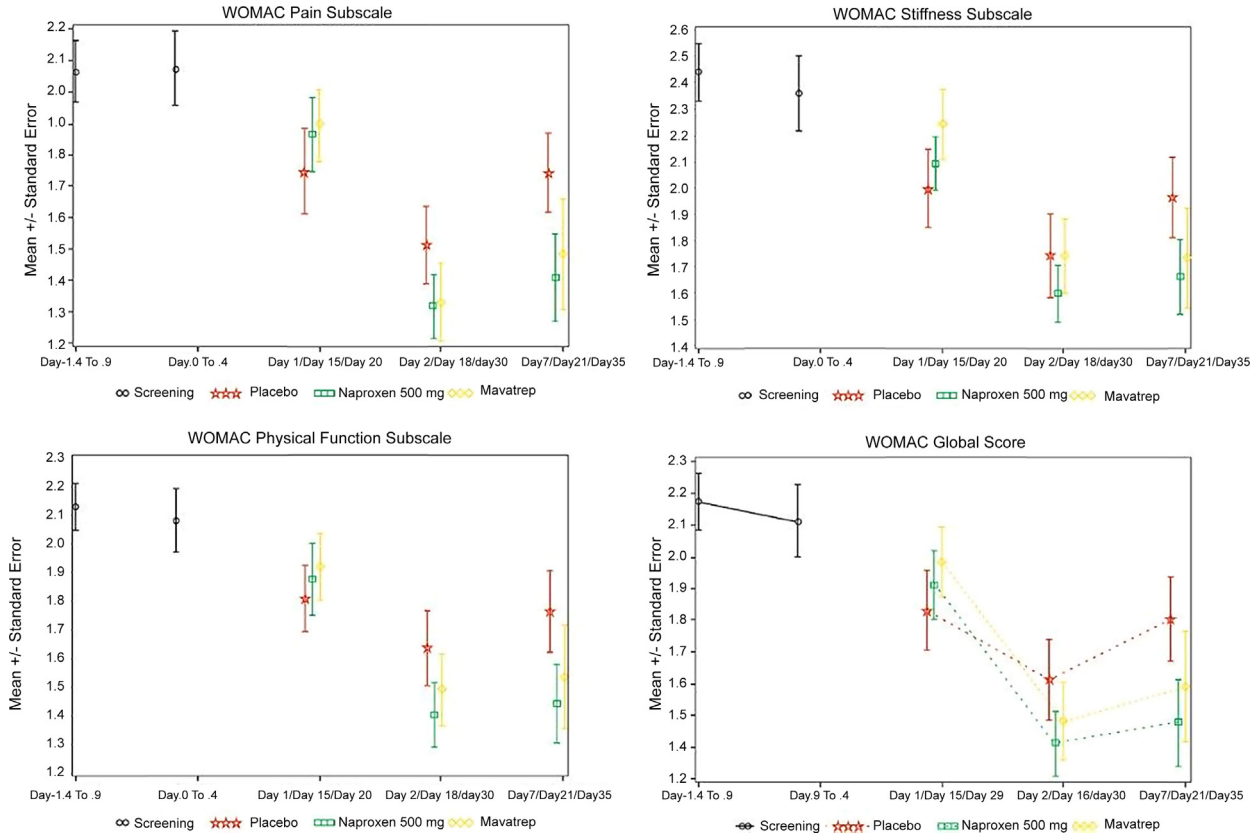

Fig. 2. WOMAC: mean +/− 1SE observed (safety analysis set).

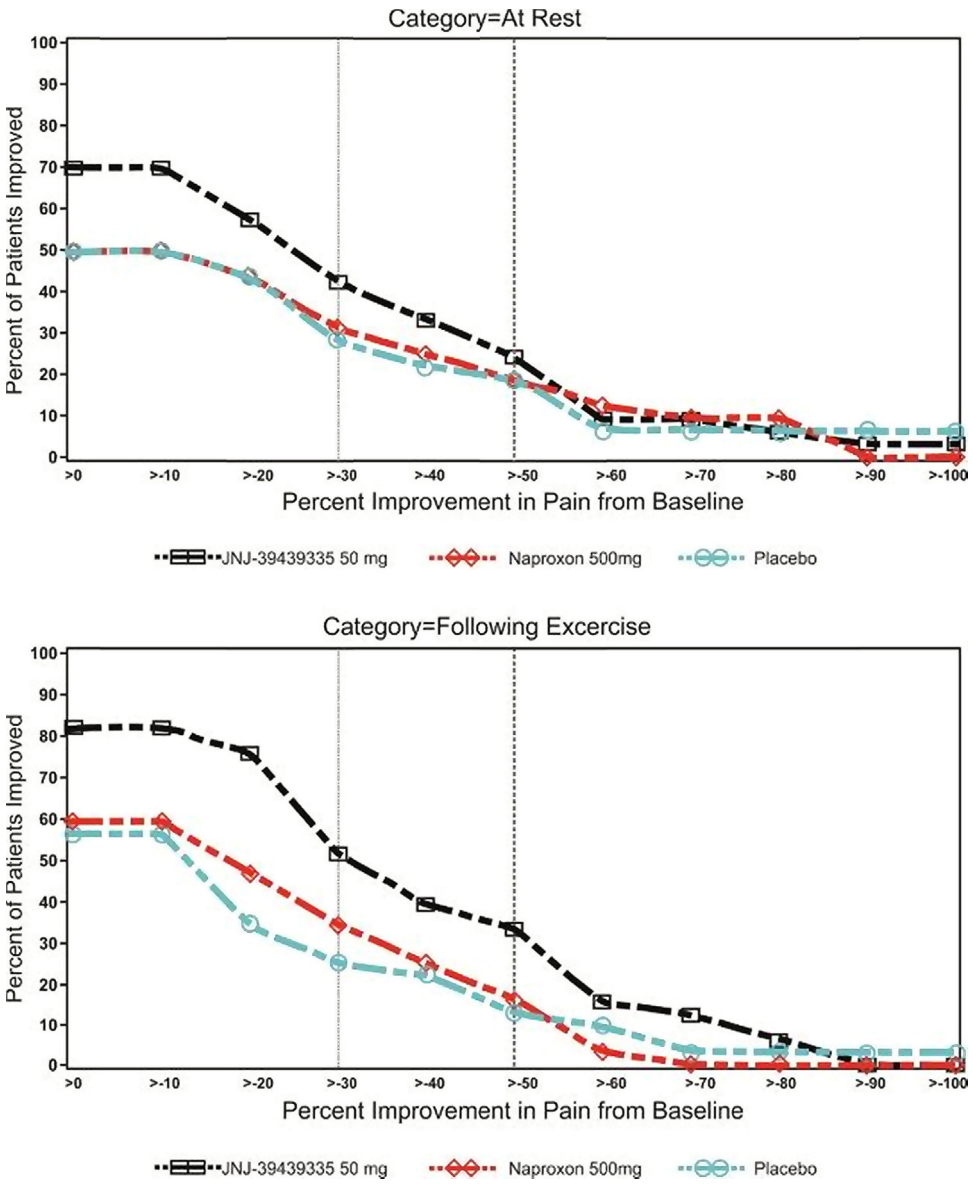

Fig. 3. Responder analyses – after stair-climbing procedure and at rest (day 1 – 4-h postdose NRS).

Fig. 3. A higher percentage of patients treated with mavatrep experienced a moderate or substantial improvement in pain at rest and after exercise at 4-h postdose compared with naproxen or placebo. A higher percentage of patients treated with naproxen compared to placebo experienced a moderate or substantial improvement in pain at rest and after exercise at 4-h postdose.

3.8. Pharmacokinetic results

Plasma samples were analyzed using a validated LC–MS/MS with quantitation range of 1.0–1000 ng/mL, and lower limit of quantitation of 1.0 ng/mL. Mavatrep concentrations at 6-h postdose ranged from 7.19 to 108 ng/mL with a mean (SD) value of 49.3 (23.8) ng/mL. Due to the long $t_{1/2}$ (57.9–125.9 h) [20], low concentrations of mavatrep were carried over to naproxen and placebo treatment periods in some patients. In most cases, mavatrep concentrations were below the limit of quantitation. However, a few patients had low mavatrep concentrations in the naproxen treatment period (maximum concentration: 18.2 ng/mL) and the placebo treatment period (maximum concentration: 11.0 ng/mL). Measurable concentrations of mavatrep during the naproxen and placebo treatments were found in 14 and 12 patients, respectively. However, statistical testing revealed no statistically significant carryover effects in the study.

3.9. Safety results

All 33 (100%) patients receiving mavatrep reported at least 1 TEAE as compared to 13 (41%) of 32 patients receiving placebo and 14 (44%) of 32 patients receiving naproxen. The most common (≥10%) TEAEs of mavatrep were mainly related to the mechanism of action as a TRPV1 antagonist, including feeling cold (79%), thermohypoesthesia (61%), dysgeusia (58%), paraesthesia (36%), and feeling hot (15%) (Table 4). Treatment-emergent minor thermal burns were experienced by 3 (9%) out of 33 patients receiving mavatrep (one patient each experienced: burnt roof of mouth on food, burn on right forearm, burned bottom lip drinking cup of tea). All thermal burns were mild and resolved without clinical sequelae.

Table 4
Common treatment-emergent adverse events (≥5%) (safety analysis set).

Body system or organ class	Placebo (*N* = 32), *n* (%)	Naproxen 500 mg (*N* = 32), *n* (%)	Mavatrep 50 mg (*N* = 33), *n* (%)	Total (*N* = 33), *n* (%)
Total number of patients with adverse events	13 (41)	14 (44)	33 (100)	33 (100)
Nervous system disorders	5 (16)	3 (9)	30 (91)	30 (91)
Thermohypoaesthesia	1 (3)	0	20 (61)	21 (64)
Dysgeusia	1 (3)	1 (3)	19 (58)	19 (58)
Paraesthesia	2 (6)	0	12 (36)	13 (39)
Dizziness	1 (3)	1 (3)	3 (9)	5 (15)
Headache	2 (6)	1 (3)	4 (12)	5 (15)
Hypoaesthesia	0	0	2 (6)	2 (6)
General disorders and administration site conditions	5 (16)	4 (13)	27 (82)	27 (82)
Feeling cold	3 (9)	2 (6)	26 (79)	26 (79)
Feeling hot	0	2 (6)	5 (15)	6 (18)
Gastrointestinal disorders	4 (13)	7 (22)	7 (21)	14 (42)
Paraesthesia oral	0	0	5 (15)	5 (15)
Diarrhoea	0	2 (6)	1 (3)	3 (9)
Dyspepsia	0	2 (6)	0	2 (6)
Vomiting	2 (6)	0	0	2 (6)
Skin and subcutaneous tissue disorders	1 (3)	1 (3)	9 (27)	10 (30)
Hyperhidrosis	1 (3)	0	2 (6)	3 (9)
Night sweats	0	0	2 (6)	2 (6)
Pruritus	0	0	2 (6)	2 (6)
Vascular disorders	1 (3)	2 (6)	4 (12)	7 (21)
Hot flush	1 (3)	1 (3)	1 (3)	3 (9)
Peripheral coldness	0	1 (3)	2 (6)	3 (9)
Musculoskeletal and connective tissue disorders	1 (3)	0	3 (9)	4 (12)
Arthralgia	1 (3)	0	1 (3)	2 (6)
Injury, poisoning and procedural complications	0	0	3 (9)	3 (9)
Thermal burns	0	0	3 (9)	3 (9)
Infections and infestations	0	2 (6)	0	2 (6)
Nasopharyngitis	0	2 (6)	0	2 (6)

Note: Percentages calculated with the number of patients in each group as denominator.
No clinically significant changes from baseline were observed in mean serum haematology, vital signs, ECG recordings, or other clinical laboratory parameters.

No deaths or serious AEs were observed during the study. There were no discontinuations due to AEs. One patient had a body temperature of 38 °C at 2 h post-mavatrep dosing that returned to the normal range at 4- and 6-h postdose.

4. Discussion

A single dose of mavatrep was associated with a significant reduction in pain compared with placebo in a stair-climbing induced pain model in patients with knee OA, which was consistent with the results of previous preclinical studies [26,27]. The pain relief associated with mavatrep in this model was evident at the first assessment (2 h postdose). Prolonged analgesic effect of mavatrep was expected due to its known long plasma half-life (57.9–125.9 h) and prolonged pharmacodynamic effects on the heat pain perception threshold [20]. To our knowledge, this is the first report of analgesic efficacy of a TRPV1 antagonist in a chronic pain condition such as OA. Notably, the staircase procedure was successful in improving the discrimination of active drug from placebo, compared to the usual evaluation of rest pain.

It is interesting to speculate why movement-evoked pain is more sensitive in demonstrating analgesic effects (vs placebo) than rest pain. This characteristic has been appreciated in clinical research for decades, and applies to dental pain (pain during opening the mouth), episiotomy (pain during sitting), abdominal surgery (pain during coughing), and knee OA. The movement increases pain intensity and the experience of evoked pain is more consistent in intensity compared to rest pain. We could think of two probable reasons why significant group effects were observed for movement-evoked pain in this study: (1) movement increases pain intensity (higher pain generally distinguishes better than low pain), and (2) the pain experience of evoked pain is more consistent in intensity than rest pain.

In addition to the assessment of evoked pain on day 1 using the staircase procedure, the WOMAC was administered on days 2 and 7 to assess patient pain. Consistent with the effects observed in the staircase model, a single dose of mavatrep administered on day 1 was associated with statistically significant improvement in pain at days 2 and 7 as compared to placebo. These results were consistent with the active comparator naproxen administered twice daily through day 7. Notably, the staircase procedure was successful at demonstrating the early time course of efficacy compared to placebo, in contrast to the WOMAC, which at best requires a 24 h recall period. While mavatrep was not superior to naproxen based on the WOMAC, it is likely that the dose regimen used in this study was not optimal therefore, may not fully reflect the therapeutic potential of mavatrep relative to standard analgesic medications. Future studies employing optimal dose regimens of mavatrep and appropriate active comparators will be needed to clarify this.

Only knee OA patients were included in this study to ensure a relatively homogeneous study population. In addition, the robust results demonstrated in the current study might be attributed, at least partly, to the use of the FAST procedure that allows excluding patients who are unable to report their perceived pain in response to the experimental thermal stimuli in an accurate and reliable fashion. As demonstrated earlier [10], patients' ability to accurately and reliably report their pain in response to the FAST is correlated with their ability to report changes in their clinical pain, thus

contributing to less "noise" in the outcome data, which in turn increases study power.

Plasma concentrations at 6 h post dose observed in this study (7.19–108 ng/mL) were within the plasma concentrations range (9 and 271 ng/mL) required to produce 80% of the maximum response (EC80) values in the carrageenan and complete Freund's adjuvant (CFA) models (data not shown). The low residual concentrations of mavatrep in some patients did not impact the ability of the study to detect statistically significant differences between treatment groups, and statistical testing revealed no statistically significant carryover effects in the study.

Safety and tolerability results were consistent with that observed in previous clinical studies with mavatrep and other TRPV1 receptor antagonists [28,29]. The AEs observed were expected based on the mechanism of action of TRPV1 antagonism, including subjective reports of feeling hot and changes in heat perception. Reporting of dysgeusia will require further study as the TRPV1 receptor has been implicated in peripheral taste cell signalling [30]. Other sensory AEs such as paraesthesia will likewise require further study with chronic dosing in patients to better understand their significance. The decreased heat perception that was associated with minor thermal burns in this study has been reported for other TRPV1 antagonists [8,31,32]. Larger clinical trials using lower multiple doses are needed with additional implementation and evaluation of patient counselling methods to determine whether the incidence of the minor thermal burns observed with mavatrep treatment can be reduced.

The limitations of this study are mainly related to its nature as a signal detection study, in that only a single administration and dose level of mavatrep was tested and therefore it is not possible to assess either the safety or efficacy (and therefore cost-benefit) of chronic administration of the compound, which is its intended use. Also, the primary endpoint in this study was based on the hypothesis that pain after stair-climbing would be more sensitive to analgesic effects compared to pain at rest, however, it may be possible that a single dose of naproxen is insufficient to observe effects in this model.

In conclusion, a single dose of mavatrep was associated with a significant reduction in pain compared with both placebo and naproxen based on the primary efficacy endpoint in a novel model of stair-climbing-induced pain in patients with OA. The effects of the known analgesic naproxen, administered twice daily for seven days, were similar to a single dose of mavatrep, suggesting clinical relevance of this stair-climbing-induced pain model for the assessment of novel analgesics for the treatment of OA pain. Mavatrep's safety profile was consistent with its mechanism of action as a TRPV1 antagonist. Further efficacy studies with a longer duration of dosing will be required to evaluate the efficacy and benefit-risk profile of mavatrep. Still to be explored is whether lower multiple doses of mavatrep can produce analgesic efficacy while minimizing adverse events, as well as the potential for improved patient counselling techniques to reduce the minor thermal burns related to decreased heat perception.

Previous presentation

The partial data from this study were presented as a poster at the 14th World Congress on Pain, Milan, Italy, 2012.

Ethical issues

The Independent Ethics Committee (Leeds [West] Research Ethics Committee, United Kingdom) and Medicines and Healthcare Products Regulatory Agency approved the protocol, and the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. All patients provided written informed consent before enrollment.

Conflict of interest

This study was funded by Janssen Research & Development, LLC, New Jersey, USA. Drs. Arthur J. Mayorga, Prasarn Manitpisitkul, Gary Romano, Christopher M. Flores, Kevin Shalayda, Mary Ellen Frustaci and John A. Moyer are employed by Janssen Research & Development. All authors meet ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors had access to the study data and made the final decision about where to publish these data.

Acknowledgement

The authors thank Rishabh Pandey (SIRO Clinpharm Pvt. Ltd.) for writing assistance and Dr. Ellen Baum (Janssen Research & Development, LLC) for additional editorial assistance. The authors also thank the study participants, without whom this study would not have been accomplished.

References

[1] Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med 2010;26:355–69, http://dx.doi.org/10.1016/j.cger.2010.03.001.

[2] Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. Lancet Lond Engl 2005;365:965–73, http://dx.doi.org/10.1016/S0140-6736(05)71086-2.

[3] Harris H, Crawford A. Recognizing and managing osteoarthritis. Nursing (Lond) 2015;45:36–42, http://dx.doi.org/10.1097/01.NURSE.0000458918.87973.15, quiz 42–3.

[4] Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. Osteoarthritis Cartilage 2007;15:981–1000, http://dx.doi.org/10.1016/j.joca.2007.06.014.

[5] Parsons WH, Calvo RR, Cheung W, Lee YK, Patel S, Liu J, Youngman MA, Dax SL, Stone D, Qin N, Hutchinson T, Lubin ML, Zhang SP, Finley M, Liu Y, Brandt MR, Flores CM, Player MR. Benzo[d]imidazole transient receptor potential vanilloid 1 antagonists for the treatment of pain: discovery of trans-2-(2-{2-[2-(4-trifluoromethyl-phenyl)-vinyl]-1H-benzimidazol-5-yl}-phenyl)-propan-2-ol (mavatrep). J Med Chem 2015;58:3859–74, http://dx.doi.org/10.1021/acs.jmedchem.5b00132.

[6] Bölcskei K, Helyes Z, Szabó A, Sándor K, Elekes K, Németh J, Almási R, Pintér E, PethoG, Szolcsányi J. Investigation of the role of TRPV1 receptors in acute and chronic nociceptive processes using gene-deficient mice. Pain 2005;117:368–76, http://dx.doi.org/10.1016/j.pain.2005.06.024.

[7] Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR, Koltzenburg M, Basbaum AI, Julius D. Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science 2000;288:306–13.

[8] Chizh BA, O'Donnell MB, Napolitano A, Wang J, Brooke AC, Aylott MC, Bullman JN, Gray EJ, Lai RY, Williams PM, Appleby JM. The effects of the TRPV1 antagonist SB-705498 on TRPV1 receptor-mediated activity and inflammatory hyperalgesia in humans. Pain 2007;132:132–41, http://dx.doi.org/10.1016/j.pain.2007.06.006.

[9] Honore P, Wismer CT, Mikusa J, Zhu CZ, Zhong C, Gauvin DM, Gomtsyan A, El Kouhen R, Lee C-H, Marsh K, Sullivan JP, Faltynek CR, Jarvis MF. A-425619 [1-isoquinolin-5-yl-3-(4-trifluoromethyl-benzyl)-urea], a novel transient receptor potential type V1 receptor antagonist, relieves pathophysiological pain associated with inflammation and tissue injury in rats. J Pharmacol Exp Ther 2005;314:410–21, http://dx.doi.org/10.1124/jpet.105.083915.

[10] Trudeau J, Katz N, Eaton T, Gracely R, Raymond S, Jensen M, Baird J, Bhat G, Ng D, Tan K, Osgood E. Predicting variability in pain reporting by psychological and psychophysical assessment. Glasgow, Scotland, UK; 2008.

[11] Pogatzki-Zahn EM, Shimizu I, Caterina M, Raja SN. Heat hyperalgesia after incision requires TRPV1 and is distinct from pure inflammatory pain. Pain 2005;115:296–307, http://dx.doi.org/10.1016/j.pain.2005.03.010.

[12] Quiding H, Jonzon B, Svensson O, Webster L, Reimfelt A, Karin A, Karlsten R, Segerdahl M. TRPV1 antagonistic analgesic effect: a randomized study of AZD1386 in pain after third molar extraction. Pain 2013;154:808–12, http://dx.doi.org/10.1016/j.pain.2013.02.004.

[13] Remadevi R, Szallisi A. Adlea (ALGRX-4975), an injectable capsaicin (TRPV1 receptor agonist) formulation for longlasting pain relief. IDrugs Investig Drugs J 2008;11:120–32.
[14] Svensson O, Thorne C, Miller F, Bjornsson M, Reimfelt A, Karlsten R. A phase II randomized controlled trial evaluating efficacy and safety of the TRPV1 antagonist AZD1386 in osteoarthritis of the knee, Montreal, Canada; 2010.
[15] Joshi SK, Honore P, Hernandez G, Schmidt R, Gomtsyan A, Scanio M, Kort M, Jarvis MF. Additive antinociceptive effects of the selective Nav1.8 blocker A-803467 and selective TRPV1 antagonists in rat inflammatory and neuropathic pain models. J Pain Off J Am Pain Soc 2009;10:306–15, http://dx.doi.org/10.1016/j.jpain.2008.09.007.
[16] Walker KM, Urban L, Medhurst SJ, Patel S, Panesar M, Fox AJ, McIntyre P. The VR1 antagonist capsazepine reverses mechanical hyperalgesia in models of inflammatory and neuropathic pain. J Pharmacol Exp Ther 2003;304:56–62, http://dx.doi.org/10.1124/jpet.102.042010.
[17] Kanai Y, Nakazato E, Fujiuchi A, Hara T, Imai A. Involvement of an increased spinal TRPV1 sensitization through its up-regulation in mechanical allodynia of CCI rats. Neuropharmacology 2005;49:977–84, http://dx.doi.org/10.1016/j.neuropharm.2005.05.003.
[18] Christoph T, Gillen C, Mika J, Grünweller A, Schäfer MK, Schiene K, Frank R, Jostock R, Bahrenberg G, Weihe E, Erdmann VA, Kurreck J. Antinociceptive effect of antisense oligonucleotides against the vanilloid receptor VR1/TRPV1. Neurochem Int 2007;50:281–90, http://dx.doi.org/10.1016/j.neuint.2006.8.017.
[19] Pomonis J, Harrison J, Mark L, Bristol D, Valenzano K, Walker K. N-(4-tertiarybutylphenyl)-4-(3-cholorphyridin-2-Yl)tetrahydropyrazine-1(2 h)-carbox-amide (BCTC), a novel, orally effective vanilloid receptor 1 antagonist with analgesic properties: II, in vivo characterization in rat models of inflammatory and neuropathic pain. J Pharmacol Exp Ther 2003;306:387–93, http://dx.doi.org/10.1124/jpet.102.046268.
[20] Manitpisitkul P, Brandt M, Flores CM, Kenigs V, Moyer JA, Romano G, Shalayda K, Mayorga AJ. TRPV1 antagonist JNJ-39439335 (mavatrep) demonstrates proof of pharmacology in healthy men: a first-in-human, double-blind, placebo-controlled, randomized, sequential group study. PAIN Rep 2016;1:e576, http://dx.doi.org/10.1097/PR9.0000000000000576.
[21] Gavva NR. Body-temperature maintenance as the predominant function of the vanilloid receptor TRPV1. Trends Pharmacol Sci 2008;29:550–7, http://dx.doi.org/10.1016/j.tips.2008.08.003.
[22] Treister R, Eaton TA, Trudeau JJ, Elder H, Katz NP. Development and preliminary validation of the focused analgesia selection test to identify accurate pain reporters. J Pain Res 2017;2017:319–26, http://dx.doi.org/10.2147/JPR.S121455.
[23] Bieleman HJ, Oosterveld FGJ, Oostveen JCM, Reneman MF, Groothoff JW. Work participation and health status in early osteoarthritis of the hip and/or knee: a comparison between the cohort hip and cohort knee and the osteoarthritis initiative. Arthritis Care Res 2010;62:683–9, http://dx.doi.org/10.1002/acr.20112.
[24] Bellamy N, Campbell J, Hill J, Band P. A comparative study of telephone versus onsite completion of the WOMAC 3.0 osteoarthritis index. J Rheumatol 2002;29:783–6.
[25] Littell R, Stroup W, Freund R. SAS® for Linear Models. 4th ed. Cary, NC, USA: SAS Institute; 2002.
[26] Luo Z, Ma L, Zhao Z, He H, Yang D, Feng X, Ma S, Chen X, Zhu T, Cao T, Liu D, Nilius B, Huang Y, Yan Z, Zhu Z. TRPV1 activation improves exercise endurance and energy metabolism through PGC-1α upregulation in mice. Cell Res 2012;22:551–64, http://dx.doi.org/10.1038/cr.2011205.
[27] Puttfarcken PS, Han P, Joshi SK, Neelands TR, Gauvin DM, Baker SJ, Lewis LGR, Bianchi BR, Mikusa JP, Koenig JR, Perner RJ, Kort ME, Honore P, Faltynek CR, Kym PR, Reilly RM. A-995662 [(R)-8-(4-methyl-5-(4-(trifluoromethyl)phenyl)oxazol-2-ylamino)-1,2,3,4-tetrahydronaphthalen-2-ol], a novel, selective TRPV1 receptor antagonist, reduces spinal release of glutamate and CGRP in a rat knee joint pain model. Pain 2010;150:319–26, http://dx.doi.org/10.1016/j.pain.2010.05.015.
[28] Round P, Priestley A, Robinson J. An investigation of the safety and pharmacokinetics of the novel TRPV1 antagonist XEN-D0501 in healthy subjects. Br J Clin Pharmacol 2011;72:921–31, http://dx.doi.org/10.1111/j.1365-2125.2011.04040.x.
[29] Schaffler K, Reeh P, Duan WR, Best AE, Othman AA, Faltynek CR, Locke C, Nothaft W. An oral TRPV1 antagonist attenuates laser radiant-heat-evoked potentials and pain ratings from UV(B)-inflamed and normal skin. Br J Clin Pharmacol 2013;75:404–14, http://dx.doi.org/10.1111/j.1365-2125.2012.04377.x.
[30] Medler KF. Multiple roles for TRPs in the taste system: not your typical TRPs. Adv Exp Med Biol 2011;704:831–46, http://dx.doi.org/10.1007/978-94-007-0265-3_43.
[31] Crutchlow M. Pharmacological inhibition of TRPV1 impairs sensation of potentially injurious heat in healthy subjects. United States: National Harbor; 2009.
[32] Rowbotham MC1, Nothaft W, Duan WR, Wang Y, Faltynek C, McGaraughty S, Chu KL, Svensson P. Oral and cutaneous thermosensory profile of selective TRPV1 inhibition by ABT-102 in a randomized healthy volunteer trial. Pain 2011;152:1192–200, http://dx.doi.org/10.1016/j.pain.2011.01.051.