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

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## 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).

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## 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

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[$p = 0.077$]). 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 nonopioid 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