



# TRPV1 antagonist JNJ-39439335 (mavatrep) demonstrates proof of pharmacology in healthy men: a first-in-human, double-blind, placebo-controlled, randomized, sequential group study

Prasarn Manitpisitkul, Michael Brandt, Christopher M. Flores, Velga Kenigs, John A. Moyer, Gary Romano, Kevin Shalayda, Arthur J. Mayorga\*

## Abstract

This double-blind, randomized, placebo-controlled, sequential group, phase 1 study was designed to assess in healthy men, the safety, tolerability, pharmacokinetics, and translational pharmacodynamics of JNJ-39439335 (mavatrep), a transient receptor potential vanilloid subtype 1 antagonist; it was preceded by a translational preclinical study which assessed the ability of JNJ-39439335 to block capsaicin-induced flare in rats, providing predictive pharmacokinetic and pharmacodynamic data that informed the subsequent phase 1 clinical study. The clinical study consisted of 2 parts: part 1 assessed pharmacokinetics and pharmacodynamics, including heat pain detection threshold and heat pain tolerance, of JNJ-39439335, and part 2 assessed pharmacodynamic effect of JNJ-39439335 on capsaicin-induced flare and sensory testing on naïve and UVB-sensitized skin in humans. Plasma concentrations of JNJ-39439335 peaked at approximately 2 to 4 hours postdose, then declined multiexponentially, with a prolonged terminal phase (half-life: 30–86 hours). Renal clearance of JNJ-39439335 was negligible. JNJ-39439335 treatment resulted in clear, consistent dose-related increases in heat pain detection threshold, heat pain tolerance, and heat pain latency. JNJ-39439335 reduced the capsaicin-induced flare area and flare intensity, with complete blocking observed in the 50-mg dose group at 144 hours postdose. This was consistent with the capsaicin flare results observed with JNJ-39439335 in rats. The most common adverse events observed in the clinical study were related to increases in body temperature after JNJ-39439335 treatment; these were predominately mild to moderate in severity with no evidence of exposure dependence up to 225 mg. JNJ-39439335 was well tolerated at single doses up to 225 mg, recommending its suitability for further clinical development.

**Keywords:** Capsaicin-induced flare, JNJ-39439335, Heat pain detection, Mavatrep, Pharmacokinetics, Pharmacodynamics, TRPV1 receptor antagonist, Single ascending dose

## 1. Introduction

Given the limitations of currently available treatments for nociceptive and neuropathic pain, a clear need exists for analgesics with novel mechanisms of action such as transient receptor potential vanilloid subtype 1 (TRPV1) antagonists.

*Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.*

Neuroscience Department, Janssen Research & Development, LLC, Titusville, NJ, USA

\*Corresponding author. Address: Neuroscience Department, Janssen Research & Development, LLC, NJ 08560. Tel.: 609-730-6779; fax: 609-730-6587. E-mail address: amayorga@its.jnj.com (A.J. Mayorga).

Copyright © 2016 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of The International Association for the Study of Pain. All rights reserved. This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0 (CC BY-ND) which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

PR9 1 (2016) e576

<http://dx.doi.org/10.1097/PR9.0000000000000576>

Although to date, all clinically tested TRPV1 antagonists block heat-induced pain specifically based on one aspect of their mechanism of action, this has not been deemed a beneficial effect of this class of agents because heat-induced pain is not a clinical condition and blockade of heat pain may predispose the participants to the risk of thermal burns. However, TRPV1 is a polymodal nociceptor that is activated not only by heat but also by a wide variety of exogenous and endogenous compounds as well as by low pH. Moreover, it is not known precisely what are the principal endogenous chemical TRPV1 activators that may be responsible for producing pain in a given pathophysiological condition, particularly at sites (eg, central nervous system) where heat is an unlikely agonist, although multiple classes of lipids have been proposed, including several metabolites of arachidonic acid and linoleic acid, endocannabinoids, and fatty acid–dopamine conjugates.<sup>6</sup> At this time, the breadth of antagonism by JNJ-39439335, and indeed all clinically tested TRPV1 antagonists to date, across the full range of purported endogenous TRPV1 activators is unknown; thus, the full spectrum of TRPV1 antagonist–mediated analgesia in humans remains to be

determined. Therefore, the advancement of TRPV1 antagonists into clinical trials and ultimately testing in pain patients is important to determine whether these agents have efficacy in clinical pain syndromes such as osteoarthritis.

JNJ-39439335 (mavatriptan) is a potent, selective, competitive TRPV1 antagonist being developed for the treatment of pain.<sup>13</sup> Consistent with the role of other TRPV1 antagonists in nociceptive hypersensitivity and inflammatory sensory sensitization,<sup>1,2,5,9,11,14</sup> preclinical studies in rat have demonstrated that JNJ-39439335 significantly attenuated carrageenan-evoked thermal hyperalgesia and complete Freund's adjuvant-evoked thermal hyperalgesia.<sup>13</sup> The compound exhibited favorable pharmacokinetic properties across species (absolute bioavailability in mice, rats, dogs, and monkeys at 10 mg/kg was 17.6% to 53.1%) and acceptable safety margins in both rat and dog 4-week toxicology studies. Preclinical studies in guinea pigs and dogs also demonstrated that JNJ-39439335 induced no direct adverse cardiohemodynamic and cardio-electrophysiological effects at exposures above the estimated therapeutic plasma levels (data not shown). Based on this preclinical efficacy and safety profile, JNJ-39439335 shows promise as a novel analgesic for clinical use.

A preclinical study was conducted to evaluate the ability of the JNJ-39439335 to block capsaicin-induced flare in rats thus providing a translational biomarker which informed clinical dose selection and study design. Subsequently, first-in-human studies were conducted to explore the safety, tolerability, and pharmacokinetics of JNJ-39439335 after oral administration of single ascending doses (SADs) in healthy men. These clinical studies also assessed the pharmacodynamic effects of single oral doses of JNJ-39439335 on capsaicin-induced flare, warm detection threshold, heat pain detection (HPD) threshold, heat pain tolerance (HPT), and mechanical pain detection threshold on naïve skin as well as warm detection threshold, HPD threshold, HPT, mechanical pain detection threshold, and mechanical allodynia on UVB-sensitized skin.

## 2. Methods

### 2.1. Preclinical study

Male, Sprague Dawley rats from Charles Rivers Laboratories (Portage, ME), weighing between 175 and 350 grams, were used for the capsaicin-induced flare studies. All animals were subjected to a week of quarantine/acclimation period before the experiment.

Animal maintenance and research were conducted in accordance with the National Research Council's policies and guidelines for the handling and use of laboratory animals outlined in the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996). Research protocols were approved by the Johnson & Johnson Pharmaceutical Research & Development LLC Institutional Animal Care and Use Committee in accordance with the guidelines of the Committee for Research and Ethical Issues of the International Association for the Study of Pain.

Animals were maintained with original cagemates throughout the study period (4 rats per cage; cages were Nalgene with corn cob bedding). Animals from several cages were randomly assigned across treatment groups.

Initial studies were conducted to characterize the effects of topical capsaicin alone. Approximately 30 minutes before capsaicin topical application, rats were anesthetized with

isoflurane, the lower abdominal skin was hair clipped, and a preliminary Doppler image was taken for determining placement of a rubber O-ring (# 7 O-Ring; 1/2" outer diameter, 3/8" inner diameter, 1/16" thickness; Danco Inc). Preferential placement of the O-ring was on an area of skin that had low blood flow, as visually assessed by laser Doppler flux units. A small amount of vaseline was used to seal the O-ring to the skin to prevent leakage of the topically administered capsaicin. Capsaicin (0.1–3 mg) or vehicle (30% ethyl alcohol, 20% Tween, and 80% and 50% sterile water) was pipetted into the O-ring in a volume of 50  $\mu$ L. Preliminary studies demonstrated that these solutions were absorbed within 15 minutes. Flare was assessed using a laser Doppler imager to obtain scans of dermal blood flow.<sup>3</sup> Scans were obtained every 15 minutes for 120 minutes after capsaicin application.

Based on the capsaicin-alone results, a total dose of 1 mg capsaicin was selected to evaluate the effect of JNJ-39439335 on capsaicin flare. JNJ-39439335 (0.3–10 mg/kg) or vehicle (20% hydroxypropyl-beta-cyclodextrin) was administered orally to rats ( $n = 6$  per dose group) 100 minutes (approximate  $t_{max}$ ) before topical administration of 1 mg capsaicin. Approximately 30 minutes before capsaicin topical administration, rats were anesthetized with isoflurane, the lower abdominal skin was hair clipped, and a preliminary Doppler image was taken for determining placement of the O-ring. A baseline scan was taken 100 minutes after vehicle or compound administration, which was immediately followed by the application of 1 mg capsaicin (50  $\mu$ L of a 20 mg/mL capsaicin solution in 30% ethyl alcohol, 20% Tween, and 80% and 50% sterile water) into the O-ring. Scans were obtained every 15 minutes for 60 minutes after capsaicin application. Plasma samples were obtained immediately after the 60-min time point (ie, 160 minutes after JNJ-39439335 administration).

Changes from baseline flux were determined every 15 minutes for 1 or 2 hours. Results are expressed in total flux units subtracted from baseline or as a percent baseline calculated, using the following formula:  $([\text{flux after capsaicin} - \text{baseline flux}] / \text{baseline flux}) \times 100$ . A repeated measure two-way analysis of variance (ANOVA) was performed followed by a Bonferroni posttest for treatment comparisons. The criterion for significant differences was  $P < 0.05$ .

### 2.2. Clinical study population

The study (EudraCT number: 2008-002799-80) enrolled healthy men between 18 and 45 years (inclusive) of age, with a body mass index (BMI) of 18.5 to 30 kg/m<sup>2</sup> (inclusive) and without any history or current evidence of significant medical illness, laboratory abnormalities, or investigational findings. All participants were nonsmokers for at least 6 months before study drug administration. Participants with an oral temperature  $>37.5^{\circ}\text{C}$ , abnormal electrocardiogram (ECG) readings, history or current evidence of congenital short QT syndrome, or other significant cardiac disease or other illness at screening or day 1 were excluded from the study. Participants were prohibited from strenuous exercise, alcohol consumption, and smoking during the study. Consumption of food and beverages containing methylxanthines and quinine was prohibited from 48 hours before to 72 hours after dosing, whereas consumption of grapefruit, grapefruit juice, and Seville oranges was prohibited from 7 days before to 7 days after dosing. Participants were prohibited from using any prescription, over the counter (including nonsteroidal anti-inflammatory drugs), herbal medication (including herbal tea or garlic extract), vitamins, or mineral supplements within 14 days before study drug

administration and for the duration of the study. St. John's Wort was prohibited within 30 days of study drug administration and during the study.

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, consistent with Good Clinical Practices and applicable regulatory requirements. The study protocol was reviewed and approved by the Institutional Review Board/Independent Ethics Committee. All enrolled participants provided written consent for their participation in the study.

### 2.3. Clinical study design

The clinical study consisted of 2 parts (part 1 and part 2). Part 1 was a single-center, double-blind (DB), randomized, placebo-controlled, sequential group, SAD study aimed to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics after single oral ascending doses of JNJ-39439335, consisting of part 1a and part 1b. In part 1a, 40 healthy men were enrolled in 5 cohorts of 8 participants each. In each cohort, participants were randomly assigned to treatment with a single dose of either JNJ-39439335 ( $n = 6$ ) or placebo ( $n = 2$ ). The dose levels administered in part 1a were 1, 2, 5, 10, and 15 mg. Because of the long half-life and prolonged effects on HPD observed in part 1a, part 1b was added to extend the in-house monitoring period and increase the number of pharmacodynamic and pharmacokinetic assessments before proceeding with further dose escalation. In part 1b, 49 healthy men were enrolled in 5 cohorts of 9 to 10 participants each. In each cohort, participants were randomly assigned to treatment with a single dose of JNJ-39439335 ( $n = 5$  or  $6$ ) or placebo ( $n = 4$ ). The dose levels administered in part 1b were 15 (dose level given in part 1a was repeated), 30, 60, 120, and 225 mg. The study duration for each participant was approximately 6 and 8 weeks, respectively, for part 1a and part 1b.

Part 2 was a DB, randomized, placebo-controlled, 3-way crossover study to assess the effect of JNJ-39439335 on capsaicin-induced flare and sensory testing on naïve and UVB-sensitized skin. Twenty healthy men were enrolled, and there were 3 treatment periods for each participant. Participants were randomly assigned to a treatment sequence and received placebo or 1 of 2 doses (10 or 50 mg) of JNJ-39439335 on day 1 of each treatment period, with a minimum 2-week washout period between each treatment. The study duration for each participant in part 2 was approximately 12 weeks.

Both parts 1 (1a and 1b) and 2 consisted of 3 phases: eligibility screening, a treatment phase, and a follow-up period. Participants were screened within 28 days before day 1 to ascertain their eligibility for the study, according to the inclusion and exclusion criteria. Eligible participants were then admitted to the clinical unit on day 2. Participants received the oral dose of study drug on day 1.

### 2.4. Starting dose selection

A starting dose of 1 mg was selected for this first-in-human study, according to Food and Drug Administration (FDA) guidelines and preclinical pharmacokinetic and pharmacodynamic studies of the compound. Allometric scaling of pharmacokinetic data from mice, rats, and monkeys was used to predict human clearance and volume of distribution, and then human exposure was estimated. Consideration was given to the appropriateness of the starting dose, based on the minimum anticipated biological effect level (MABEL). JNJ-39439335 was shown to be active in

a number of preclinical models. The known characteristics of TRPV1 antagonists generally and JNJ-39439335 specifically suggest that JNJ-39439335 would not be considered a high-risk compound necessitating dosing below the minimum anticipated biological effect level in humans. However, to provide an additional level of protection to human participants, a starting dose of 1 mg, which is more than 68-fold lower than the maximum recommended starting dose, was chosen. This maximum recommended starting dose was predicted to result in plasma concentrations below the minimal effective concentrations observed in relevant preclinical in vivo assays.<sup>13</sup>

### 2.5. Dosage, administration, and dose escalation criteria

After an overnight fast (at least 10 hours), JNJ-39439335 or placebo (as a tablet formulation) was administered orally in a semirecumbent position with 240 mL of water. Participants were allowed free access to drinking water until 2 hours before study drug administration and from 2 hours after study drug administration. Water and other fluids (methylxanthine free) were allowed ad libitum throughout the study. Lunch was provided at approximately 4 hours after dose, and dinner was provided at approximately 10 hours after dose.

### 2.6. Pharmacokinetic assessments

#### 2.6.1. Sample collections and handling

Venous blood samples of 3 mL were collected for the determination of JNJ-39439335 concentrations. For part 1a, blood samples were collected at predose (within 30 minutes) and at 30 minutes, 1-, 1.5-, 2-, 3-, 4-, 5-, 6-, 8-, 10-, 12-, 16-, 24-, 36-, 48-, 72-, 96-, 120-, 144-, and 168-hour postdose. For part 1b and part 2, blood samples were collected at predose (within 30 minutes), and at 30 minutes, 1-, 1.5-, 2-, 3-, 4-, 5-, 6-, 8-, 10-, 12-, 16-, 24-, 36-, 48-, 72-, 96-, 120-, 144-, 168-, 192-, 216-, 240-, 264-, 288-, and 312-hour postdose and at the follow-up visit. Urine samples for the assessment of JNJ-39439335 concentrations were collected –18 to –14 hours (predose) and over the intervals of 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, and 96 to 120 hours after dose.

#### 2.6.2. Sample analyses

Plasma concentrations of JNJ-39439335 were determined using a validated, selective, and sensitive liquid chromatography–mass spectrometry (LC-MS/MS) method. Urine samples were analyzed by qualified liquid chromatography–mass spectrometry (LC-MS/MS) assay. Placebo samples were not analyzed, except for 2 samples per participant receiving placebo: one predose and one around the expected  $t_{max}$  (as emerging from the actual measurement of the samples of the first dose group), to ensure from a safety perspective that no additional participants were on active treatment. The range of quantification for plasma samples was from 1 to 1000 ng/mL, and the lower limit of quantification was 1 ng/mL. The range of quantification for urine samples was from 5 to 1000 ng/mL, and the lower limit of quantification was 5 ng/mL.

#### 2.6.3. Pharmacokinetic analysis

Plasma and urine drug concentrations were subjected to pharmacokinetic analysis using noncompartmental methods by WinNonlin Enterprise Version 5.2.1 (Pharsight Corporation, Mountain View, CA) and EXCEL software, Version 2007

(Microsoft Corporation, Redmond, WA). Based on the individual data, using the actual sampling times, pharmacokinetic parameters were estimated: maximum observed concentration ( $C_{\max}$ ), determined by visual inspection of the data; time to reach  $C_{\max}$  ( $t_{\max}$ ), determined by visual inspection of the data; area under the concentration–time curve from 0 to 24 hours postdose ( $AUC_{24}$ ); AUC from time 0 to infinity, calculated as  $AUC_{\infty} = AUC_{\text{last}} + C_{\text{last}}/\lambda_z$ , where  $C_{\text{last}}$  is the last observed quantifiable concentration, and  $\lambda_z$  is the terminal elimination rate constant; elimination half-life associated with the terminal slope ( $\lambda_z$ ) of the semilogarithmic drug concentration–time curve ( $t_{1/2}$ ), calculated as  $0.693/\lambda_z$ ; apparent total oral clearance after extravascular administration ( $CL/F$ ), calculated as  $\text{dose}/AUC_{\infty}$ ; apparent terminal volume of distribution after extravascular administration ( $V_z/F$ ), calculated as  $V_z/F = D/(\lambda_z \times AUC_{\infty})$ ; and mean residence time, calculated as  $AUMC/AUC$ , where AUMC is the area under the first moment of the plasma concentration–time curve from time 0 to infinity. It should be noted that all AUC extrapolation ( $AUC_{\text{last}-\infty}$ ) values were  $\leq 25\%$  of  $AUC_{\infty}$ .

In addition, the cumulative amount of unchanged drug excreted in urine ( $A_e$ ) was calculated by multiplying the urinary volume with urinary concentration.  $A_e$ , as a percent of dose (%  $A_e$ ), was calculated as  $(A_e/\text{Dose}) \times 100$ . Renal clearance ( $CL_R$ ) was calculated as a ratio of  $A_e$  to AUC.

## 2.7. Pharmacodynamic assessments

### 2.7.1. Clinical study: part 1

In part 1a, HPD threshold and HPT tests were performed on day 1 (predose and 4-hour postdose) and at follow-up. In part 1b, HPD threshold, HPT, heat pain latency, cold pain detection threshold, and mechanical pain detection threshold were performed on day –1, day 1 (predose and 4- and 8-hour postdose), day 2 (24-hour postdose), day 4 (72-hour postdose), day 6 (120-hour postdose), and at follow-up. The HPD threshold was additionally measured on days 7 through 14 (144- to 312-hour postdose).

Briefly, the HPD and HPT were assessed using a computer-controlled  $9 \times 9$ -mm Peltier device (MSA Thermostest, Somedic, Sweden). For HPD threshold, the device was positioned on the volar aspect of the forearm, approximately 20 cm from the wrist crease, and within approximately 1 cm of the midline, avoiding the area intended for capsaicin administration. The baseline temperature of the probe was  $32^{\circ}\text{C}$  and gradually increased at a rate of  $1^{\circ}\text{C}$  per second. The test was stopped, and the temperature threshold was returned to baseline by the participant by pushing a button on the response unit when the HPD (first sensation of heat pain) was reached. The maximum cutoff temperature was  $52^{\circ}\text{C}$  to avoid skin injury. The procedure for HPT was identical, except that the participants were instructed to push the button when they felt the maximum tolerable pain.

Heat pain latency, cold pain detection, and mechanical pain detection threshold were assessed after HPT assessments at predose and at the predetermined postdose times in part 1b. For the heat pain latency test, participants were asked to place the tip of their ring finger on the tip of the  $9 \times 9$ -mm Peltier device preheated to  $52^{\circ}\text{C}$  and to withdraw their hand when the heat pain was no longer tolerable; a maximum latency of 10 seconds was used to prevent skin injury. A similar method was used for cold pain detection, except that the probe temperature was gradually decreased at a rate of  $1^{\circ}\text{C}$  per second, with the cutoff temperature set at  $0^{\circ}\text{C}$ . For mechanical pain detection threshold, mechanical stimuli of increasing intensity were applied to the dorsal skin fold

between the index finger and middle finger using von Frey hairs that exerted forces of 78, 256 and 588 mN, respectively, with a 1-minute interval between the presentation of successively increasing calibers of von Frey hairs. The first von Frey hair that the participant reported as painful was recorded as the mechanical pain threshold, and the pain intensity was rated on a numerical rating scale (0–11), with 0 being no pain at all and 11 being the worst pain imaginable.

### 2.7.2. Clinical study: part 2

The effects of 2 different doses of JNJ-39439335 vs placebo were assessed on capsaicin-induced flare, warm detection threshold, HPD threshold, HPT, and mechanical pain detection threshold on naïve skin as well as warm detection threshold, HPD threshold, HPT, mechanical pain detection threshold, and mechanical allodynia on UVB-sensitized skin.

A laser Doppler imager was used to obtain a scan of dermal blood flow on an area of the forearm before and after application of capsaicin (Axsain, 0.075% capsaicin w/w). Capsaicin was kept on the skin for 30 minutes. The flare area (in  $\text{cm}^2$ ) was calculated from all pixels around the stimulation site in which flux values exceeded the 95% percentile (mean + 2 SD) of the baseline distribution. The flare intensity was calculated using relative flux (arbitrary units). Participants underwent the capsaicin flare procedure at baseline (predose), at 4-hour postdose, and on day 7 at 144-hour postdose.

On day –2, participants received varying doses of UVB light on the lower back. The erythema associated with each dose of UVB light on the lower back was assessed on day 1, and the minimal erythema dose (MED) was determined. Participants received  $3 \times$  MED of UVB light on the volar forearm on day –1. Warm detection threshold, HPD threshold, HPT, mechanical pain detection threshold, and mechanical allodynia were assessed on the  $3 \times$  MED UVB-sensitized skin as well as naïve skin on day 1 at predose, 4-, 8-, 24-, 72-, 120-, and 144-hour postdose, and at the follow-up visit. In naïve skin, HPD threshold was also assessed on days 8 through 14.

## 2.8. Safety analyses

Safety evaluations included reporting of treatment-emergent adverse events (TEAEs), clinical laboratory testing, ECG, oral temperature, vital signs, and physical examinations.

## 2.9. Statistical analysis

No formal statistical calculations of sample size were conducted for part 1 of the study. A sample size of 8 participants per group (6 active and 2 placebo) was considered sufficient to allow clinical judgment of safety and tolerability as well as pharmacokinetic assessments for the study. The number of participants receiving placebo was increased to 4 per cohort in part 1b to minimize possible bias associated with the potentially high frequency of events related to heat perception in each cohort. The sample size for part 2 of the study was based on a published study of the effects of another TRPV1 antagonist on HPD threshold and capsaicin-induced flare.<sup>3</sup> All pharmacokinetic data were summarized descriptively for both parts 1 and 2.

The analysis of HPD threshold, HPT, heat pain latency, cold pain detection threshold, and mechanical pain detection threshold assessments in part 1 was considered exploratory. A mixed-effects ANOVA model was used to compare the on-treatment assessment values of active vs placebo. In part 2, all

pharmacodynamic endpoints were evaluated at baseline and on-treatment. A mixed-effects ANOVA model appropriate for a three-period crossover study was used to compare the on-treatment assessment value of active doses vs placebo, with period and treatment as fixed effects and participants as random effect. A mixed-effects ANOVA model for postdose flare precapsaicin (corrected), with terms for period and treatment as fixed effects, patients as a random effect and the predose flare (precapsaicin corrected) as a covariate was used for flare analysis. Flare area data were log transformed before analysis and then back transformed for interpretation. For each comparison, point estimates and 95% CIs for the difference between JNJ-39439335 and placebo were constructed using the appropriate variance term. Safety was summarized descriptively. In addition, in part 1 and part 2, plasma concentrations and corresponding individual body temperature and QTcF values were plotted to evaluate their relationship. An  $E_{max}$  (maximum effect) model was fitted to describe the relationship between body temperature and plasma concentrations as well as the relationship between the decrease in QTcF and JNJ-39439335 plasma concentrations.

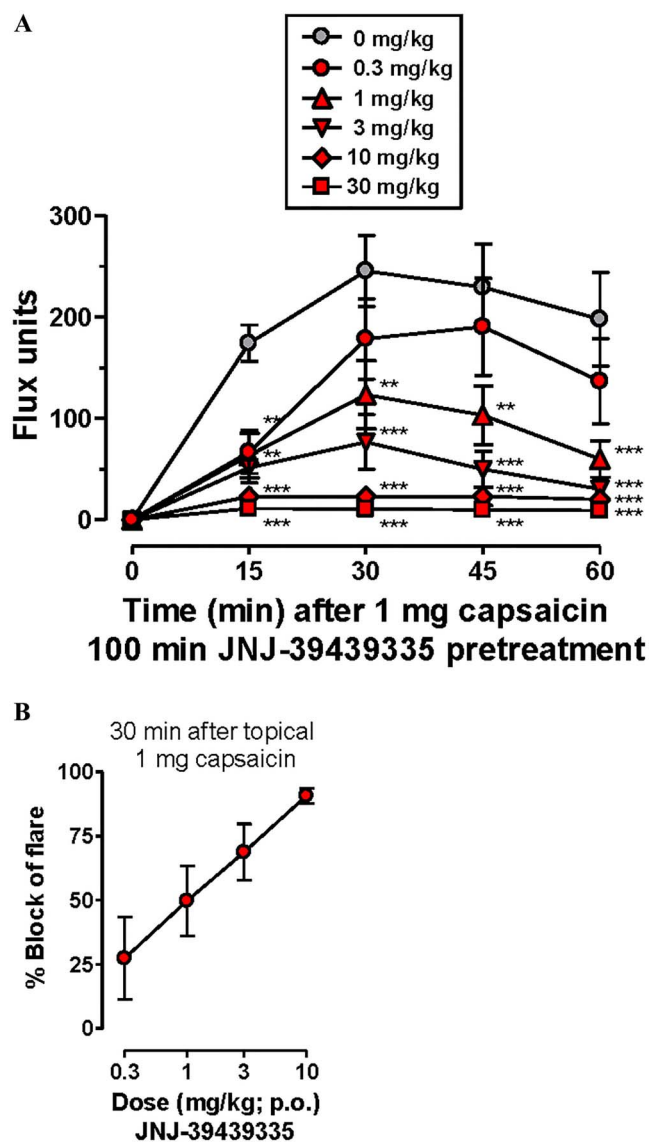
### 3. Results

#### 3.1. Preclinical capsaicin flare observations

Capsaicin-induced flare was conducted as a translational pharmacodynamic model before clinical studies. Capsaicin produced a time- and dose-dependent flare response in anesthetized rats, with the maximal flare response being observed between 30 and 45 minutes after topical application. A low dose of 0.1 mg capsaicin did not produce any increase in flare, whereas a dose of 0.3 mg produced a transient increase in flare that peaked 30 minutes after topical application. A dose of 1 mg capsaicin produced the greatest amount of flare, and larger concentrations of capsaicin did not increase flare further. As a result, 1 mg capsaicin was selected and used to evaluate the effect of JNJ-39439335 on capsaicin-induced flare. Pretreatment with JNJ-39439335 (0.3–30 mg/kg, p.o.) blocked the capsaicin-induced flare in a dose-dependent fashion (Fig. 1A), exhibiting an  $ED_{50}$  value of 1.9 mg/kg at the 30-minute time point after capsaicin treatment (Fig. 1B), which was associated with an estimated plasma exposure of  $67.6 \pm 44.9$  ng/mL (data not shown).

#### 3.2. Clinical study: demographics and baseline characteristics

This study was conducted from July 17, 2008 to October 25, 2009. In part 1, 88 of 89 participants in the safety analysis set (all participants receiving at least 1 dose of JNJ-39439335 or placebo) completed the study. The demographics and baseline characteristics of all part 1 participants were comparable across all the treatment groups: most were white (74.2%), 13.5% were black, and 6.7% were Asian; mean age of participants was 28.5 years (range, 19 to 45 years), and the mean BMI was 23.7 kg/m<sup>2</sup> (range, 19 to 30 kg/m<sup>2</sup>). One participant in the 15-mg dose cohort withdrew consent. In part 2, 19 of 20 participants in the safety analysis set completed the study. The demographics and baseline characteristics of all part 2 participants were comparable across the treatment groups. All participants were white; the mean age was 28.7 years (range, 22 to 42 years), and the mean BMI was 24.0 kg/m<sup>2</sup> (range, 21 to 28 kg/m<sup>2</sup>). One participant in part 2 was withdrawn from the study after testing positive for drugs and alcohol on day -1.



**Figure 1.** Effects of JNJ-39439335 (0.3–10 mg/kg, p.o.) on topical capsaicin (1 mg, administered 100 minutes after JNJ-39439335)-induced flare in rats; (A) plotted as flux units subtracted from baseline vs time after capsaicin administration and (B) % block of flare vs JNJ-39439335 doses. X axis: time in min after the topical application of 1.0 mg capsaicin (n=4–6). Y axis: average flux units ( $1 \pm$  SEM) with flux units subtracted from baseline. Asterisks indicate significance (\*\*=p>0.01; \*\*\*=p>0.001). X axis: oral dose in mg per kg of JNJ-39439335 (n=6) administered 130 min before laser Doppler scan (30 min after 1 mg topical capsaicin application). Y axis: percent block of flare ( $1 \pm$  SEM).

#### 3.3. Pharmacokinetic results

The concentrations of JNJ-39439335 in urine were below the quantification limit; therefore, the percentage of unchanged drug excreted in urine and renal clearance data is not presented. This indicates that JNJ-39439335 is mainly eliminated through nonrenal clearance.

##### 3.3.1. Part 1

When administered as a tablet formulation under fasted conditions, JNJ-39439335 was absorbed with median  $t_{max}$  of 2.02 to 4.44 hours after which the plasma concentrations declined multiexponentially with a mean elimination half-life of



29.9 to 85.9 hours over doses of 1 to 225 mg (Table 1 and Fig. 1). All participants receiving JNJ-39439335 showed systemic exposure ( $C_{max}$  and  $AUC_{\infty}$ ) which increased with increasing doses (Fig. 2). Dose-normalized  $C_{max}$  and dose-normalized  $AUC_{\infty}$  decreased with increasing doses, indicating less than dose-proportional increase in exposure over doses of 1 to 225 mg. Furthermore, the values for CL/F and  $Vd_z/F$  increased with increasing dose levels (Table 2).

3.3.2. Part 2

When administered as a tablet formulation under fasted conditions, JNJ-39439335 was absorbed with median  $t_{max}$  of approximately 3 hours; the plasma concentrations declined multiexponentially thereafter with a mean elimination half-life of 66.0 (10 mg dose) and 68.6 hours (50 mg dose) (Table 2 and Fig. 3). Similar to the observations in part 1, the systemic exposure to JNJ-39439335 increased with increasing doses (Fig. 3), whereas the dose-normalized  $C_{max}$  and  $AUC_{\infty}$  decreased with increasing dose.

3.4. Pharmacodynamic results

3.4.1. Part 1

The mean HPD threshold value increased from predose to postdose relative to placebo at  $\geq 10$  mg dose levels (Fig. 4). Most participants reached the cutoff temperature (52°C) at doses of  $\geq 30$  mg. Heat pain detection (HPD) threshold was maximal on the day of dosing (at the 4- or 8-hour postdose time point) and persisted onto day 14 for the 120- and 225-mg doses. These HPD threshold values returned to baseline by the follow-up assessment conducted on day 28.

Increases in mean HPT values from predose to postdose were observed at JNJ-39439335 dose levels of 2 mg and higher. Participants across treatment groups tolerated the pain induced by the maximum temperature allowed in this study (52°C) at predose, making it difficult to interpret changes from baseline.

Increases in mean heat pain latency values from predose to postdose occurred at all JNJ-39439335 dose levels tested (15 to 225 mg). Most of the participants tolerated the pain induced by the maximum temperature allowed in this study (52°C) for the maximum 10-second limit applied at predose, making it difficult to interpret changes from baseline.

No clear separation from placebo and no clear dose-related effect across the 15- to 225-mg dose range were observed for cold pain detection threshold. No clear treatment- or dose-related effects on mean mechanical pain rating values at von Frey hair levels of 78, 256, or 588 mN were observed. At all 3 von Frey hair levels, there was no clear separation from placebo and no clear dose-related effect across the 15- to 225-mg dose range.

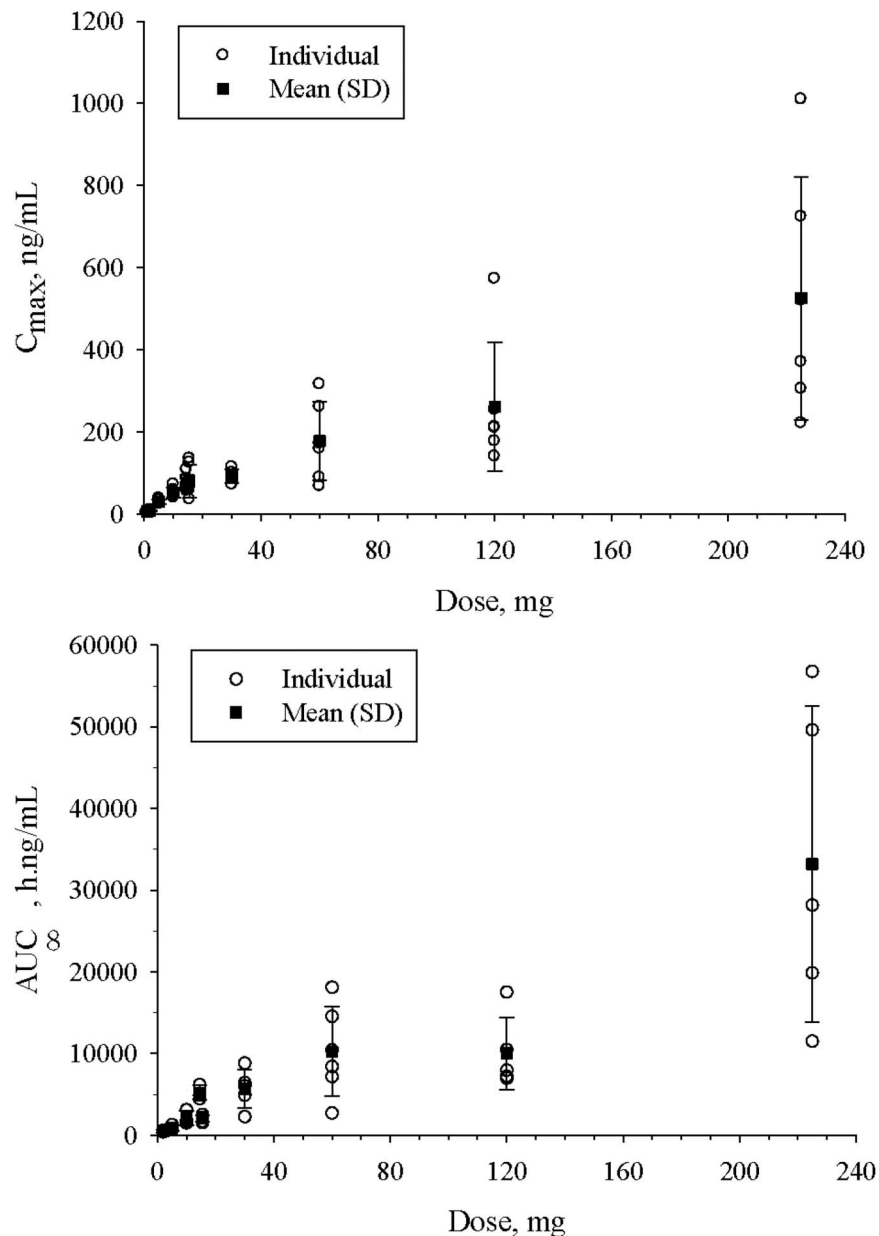
3.4.2. Part 2

A dose-related reduction in capsaicin-induced flare intensity and flare area was observed in healthy men after JNJ-39439335 administration. A clear difference vs placebo was observed for both parameters at both 4- and 144-hour postdose. Capsaicin-induced flare intensity and flare area were completely blocked at 144-hour postdose in the 50-mg dose cohort. The HPD threshold, HPT, and (to a lesser extent) warm detection threshold values at baseline were lower in participants with UVB-sensitized skin than in those with naïve skin. A dose-dependent increase in HPD threshold, HPT, and warm detection threshold was observed after

**Table 1** Mean (%CV) JNJ-39439335 pharmacokinetic parameters in healthy men after single oral of JNJ-39439335.

Treatment	$C_{max}$ , ng/mL	$t_{max}$ ,* h	$AUC_{0-4h}$ , h·ng·mL <sup>-1</sup>	$AUC_{last}$ , h·ng·mL <sup>-1</sup>	$AUC_{\infty}$ , h·ng·mL <sup>-1</sup>	$t_{1/2}$ , h	Mean residence time, h	$Vd_z/F$ , L	CL/F, L/h
<b>Part 1</b>									
1 mg (n = 6)	6.04 (22.1)	4.44 (3.02-5.00)	83.0 (24.0)	317 (42.3)	NAs	NAs	77.2 (18.3)†	NAs	NAs
2 mg (n = 6)	7.66 (15.6)	3.94 (1.98-6.00)	94.7 (24.7)	300 (49.3)	495 (28.5)†	47.8 (4.5)†	43.6 (17.9)†	289 (24.2)†	4.21 (28.5)†
5 mg (n = 6)	29.6 (19.7)	3.95 (3.00-5.00)	350 (21.3)	971 (45.6)	876 (32.2)‡	29.9 (18.1)‡	51.7 (31.6)‡	253 (12.3)‡	6.08 (25.4)‡
10 mg (n = 6)	52.1 (23.5)	3.47 (2.02-4.98)	677 (35.5)	2359 (40.2)	2109 (41.5)§	35.6 (45.0)§	84.0 (21.0)§	242 (14.1)§	5.23 (34.2)§
15 mg (n = 6)	75.9 (25.2)	3.98 (2.00-5.97)	1006 (30.1)	3780 (25.5)	5187 (17.3)§	59.3 (20.9)§	56.9 (42.3)§	250 (24.5)§	2.95 (16.2)§
15 mg R (n = 6)	79.7 (50.7)	3.45 (1.97-4.97)	879 (40.9)	1938 (18.7)¶	2014 (19.4)¶	39.4 (53.9)¶	115.9 (36.7)¶	425 (62.5)¶	7.68 (19.8)¶
30 mg (n = 6)	91.8 (17.3)	3.03 (1.98-5.00)	1052 (21.7)	5156 (39.9)	5691 (42.0)	82.6 (31.8)	91.4 (52.8)	671 (24.2)	6.48 (60.3)
60 mg (n = 6)	177 (54.4)	3.98 (2.00-5.03)	2367 (55.1)	9850 (56.3)	10,232 (53.6)	53.4 (69.6)	93.0 (50.1)¶	574 (83.7)	8.47 (82.1)
120 mg (n = 6)	261 (60.4)	3.00 (2.00-6.00)	2815 (42.7)	13,146 (74.5)	10,034 (43.9)¶	63.0 (60.3)¶	121.2 (26.6)¶	1082 (45.7)¶	13.4 (32.1)¶
225 mg (n = 6)	525 (56.5)	2.02 (1.57-5.02)	5745 (61.8)	27,910 (56.3)	33,190 (58.3)¶	85.9 (30.3)¶		1046 (47.8)¶	9.47 (67.2)¶
<b>Part 2</b>									
10 mg (n = 19)	38.6 (24.9)	3.05 (1.48-5.98)	476 (28.1)	1855 (46.7)	2039 (50.4)	66.0 (53.3)	90.7 (47.9)	505 (40.2)	7.30 (93.0)
50 mg (n = 20)	160 (26.3)	2.9 (1.50-5.17)	1753 (28.6)	7296 (34.9)	7821 (39.9)	68.6 (37.1)	99.5 (37.7)	670 (32.8)	7.44 (40.3)

\* Median (Min-Max).  
 † n = 2.  
 ‡ n = 4.  
 § n = 3.  
 ¶ n = 5.  
 NAs, not assessable.



**Figure 2.** Relationship of  $C_{max}$  and  $AUC_{\infty}$  of JNJ-39439335 in plasma vs dose in healthy men after single oral ascending doses of JNJ-39439335 (1 to 225 mg).

JNJ-39439335 administration for both naïve and UVB-sensitized skin. A clear difference vs placebo was evident for both dose levels of JNJ-39439335 at all postdose time points. UVB-sensitization appeared to wear off by day 4, as seen by an increase in these parameters in the placebo group around this time. For mechanical pain detection threshold, no clear treatment or dose-related effects were observed in naïve skin or UVB-sensitized skin.

### 3.5. Pharmacokinetic/pharmacodynamic results

#### 3.5.1. Heat pain detection threshold, heat pain tolerance, and heat pain latency (part 1)

Heat pain detection threshold, HPT, and heat pain latency values increased with increasing plasma concentrations of JNJ-39439335. Most participants reached the maximum temperature allowed in this study ( $52^{\circ}\text{C}$ ) for HPD threshold at concentrations of  $\geq 100$  ng/mL. For HPT, all participants tolerated the maximum

temperature ( $52^{\circ}\text{C}$ ) allowed in this study at JNJ-39439335 concentrations  $> 100$  ng/mL. Relative to predose, HPT increased by as much as  $4^{\circ}\text{C}$  to  $4.5^{\circ}\text{C}$  for some participants. For heat pain latency, most participants were unable to detect heat pain within the 10-second limit applied in this study with increasing JNJ-39439335 plasma concentrations. No clear pattern in cold pain detection temperature was observed vs plasma concentrations of JNJ-39439335 as most of the participants were able to detect cold pain before the minimum temperature ( $0^{\circ}\text{C}$ ) allowed in this study. There was no clear relationship between plasma concentrations and mechanical pain detection.

#### 3.5.2. Heat pain detection threshold and warm detection threshold (part 2)

The HPD threshold and warm detection threshold values increased with increasing plasma concentrations of JNJ-39439335 on naïve skin and UVB-sensitized skin. Most

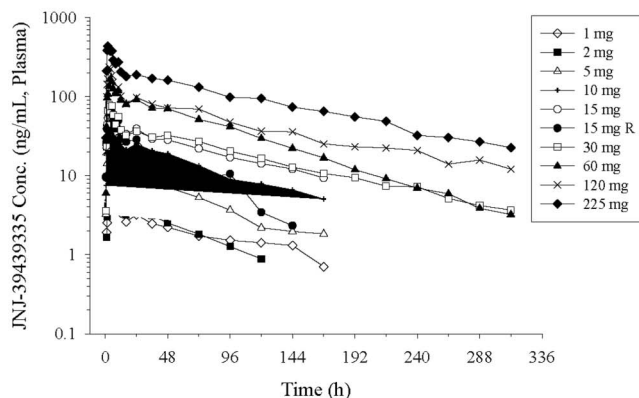
**Table 2****Treatment-emergent adverse events occurring in 2 or more participants receiving JNJ-39439335 in part 1 and 2.**

	Placebo (N = 30), n (%)	JNJ-39439335 (part 1), n (%)										Placebo (N = 20), n (%)	JNJ-39439335 (part 2), n (%)			
		1 mg (N = 6)	2 mg (N = 6)	5 mg (N = 6)	10 mg (N = 6)	15 mg (N = 6)	15 mg R (N = 6)	30 mg (N = 5)	60 mg (N = 6)	120 mg (N = 6)	225 mg (N = 6)		Total (N = 89)	10 mg (N = 19)	50 mg (N = 20)	Total (N = 20)
Total no. participants with AEs	16 (53)	2 (33)	3 (50)	4 (67)	6 (100)	6 (100)	6 (100)	5 (100)	6 (100)	6 (100)	6 (100)	66 (74)	6 (30)	17 (89)	19 (95)	20 (100)
Pyrexia	0	0	0	4 (67)	5 (83)	4 (67)	2 (33)	3 (60)	4 (67)	4 (67)	3 (50)	0	8 (42)	11 (55)	12 (60)	
Thermohypoesthesia	0	0	0	0	3 (50)	5 (83)	2 (33)	3 (60)	1 (17)	4 (67)	5 (83)	23 (26)	1 (5)	9 (47)	12 (60)	14 (70)
Feeling cold	1 (3)	0	0	1 (17)	0	4 (67)	3 (50)	5 (100)	4 (67)	1 (17)	2 (33)	21 (24)	2 (10)	9 (47)	9 (45)	13 (65)
Feeling hot	0	0	0	1 (17)	0	5 (83)	3 (50)	4 (80)	1 (17)	1 (17)	5 (83)	20 (22)	1 (5)	6 (32)	8 (40)	11 (55)
Paresthesia	0	0	0	0	1 (17)	2 (33)	2 (33)	0	0	0	3 (50)	8 (9)	0	7 (37)	9 (45)	11 (55)
Dizziness postural	2 (7)	1 (17)	0	0	2 (33)	1 (17)	0	0	0	1 (17)	0	7 (8)	1 (5)	0	1 (5)	2 (10)
Dizziness	1 (3)	0	0	0	1 (17)	1 (17)	0	1 (20)	0	1 (17)	1 (17)	6 (7)	0	0	2 (10)	2 (10)
Headache	1 (3)	0	1 (17)	0	1 (17)	0	0	0	0	1 (17)	2 (33)	6 (7)	1 (5)	3 (16)	3 (15)	5 (25)
Orthostatic hypotension	2 (7)	0	0	0	2 (33)	0	0	1 (20)	0	0 <sup>a</sup>	1 (17)	6 (7)	—	—	—	—
Burning sensation	0	0	0	0	0	0	0	0	0	0	5 (83)	5 (6)	—	—	—	—
Hyperhidrosis	0	0	0	0	1 (17)	3 (50)	0	0	0	0	1 (17)	5 (8)	1 (5)	2 (11)	2 (10)	4 (20)
Thermal burn	0	0	0	0	0	0	0	1 (20)	0	0	3 (50)	4 (4)	0	0	2 (10)	2 (10)
Pruritus	0	0	0	0	1 (17)	1 (17)	0	0	0	1 (17)	1 (17)	4 (4)	—	—	—	—
Thermal burn	0	0	0	0	0	0	0	1 (20)	0	0	3 (50)	4 (4)	—	—	—	—
Hypoesthesia	0	0	1 (17)	0	0	0	1 (17)	0	1 (17)	1 (17)	0	4 (4)	—	—	—	—
Pruritus	0	0	0	0	1 (17)	1 (17)	0	0	0	1 (17)	1 (17)	4 (4)	—	—	—	—
Nausea	0	0	0	0	1 (17)	0	0	0	1 (17)	1 (17)	0	3 (3)	—	—	—	—
Dysgeusia	0	0	0	0	0	1 (17)	0	1 (20)	1 (17)	0	0	3 (3)	0	4 (21)	5 (25)	7 (35)
Hypogeusia	0	0	0	0	0	2 (33)	0	0	0	0	0	2 (2)	—	—	—	—
Chills	0	0	0	0	0	0	0	0	0	1 (17)	1 (17)	2 (2)	—	—	—	—
Fatigue	0	1 (17)	0	0	0	0	0	0	0	1 (17)	0	2 (2)	—	—	—	—
Rhinitis	0	0	0	0	2 (33)	0	0	0	0	0	0	2 (2)	—	—	—	—
Back pain	0	0	0	0	0	0	0	2 (40)	0	0	0	2 (2)	—	—	—	—
Agusia	0	0	0	0	0	0	0	0	0	0	2 (33)	2 (2)	—	—	—	—
Hematoma	0	0	1 (17)	0	0	0	0	0	0	1 (17)	0	2 (2)	—	—	—	—
Disturbance in attention	—	—	—	—	—	—	—	—	—	—	—	—	0	1 (5)	2 (10)	2 (10)
Oropharyngeal pain	—	—	—	—	—	—	—	—	—	—	—	—	0	1 (5)	1 (5)	2 (10)

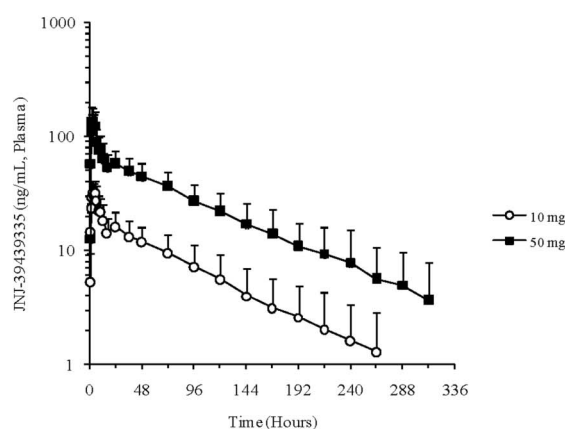
<sup>a</sup> One participant in the 120-mg dose group had an adverse event of orthostatic hypotension that was incorrectly coded as orthostatic hypertension. Therefore, the incidence of orthostatic hypotension in the 120-mg dose group should be 1 (17%). AEs, adverse events.



## Part 1



## Part 2



**Figure 3.** Mean plasma concentration–time profiles of JNJ-39439335 after single oral administration in healthy men under fasted conditions in part 1 (1 to 225 mg) and part 2 (10 and 50 mg).

participants reached the maximum HPD threshold temperature allowed in this study ( $52^{\circ}\text{C}$ ) at JNJ-39439335 concentrations  $>50$  ng/mL on naïve and UVB-sensitized skin. For HPT, most participants were able to tolerate the maximum temperature ( $52^{\circ}\text{C}$ ) allowed in this study at all measurable JNJ-39439335 concentrations on naïve skin. On UVB-sensitized skin, most participants were able to tolerate the maximum temperature at JNJ-39439335 concentrations  $>50$  ng/mL. Warm detection threshold values increased with increasing plasma concentrations of JNJ-39439335 on both naïve and UVB-sensitized skin. Most participants were able to detect warmth before reaching the maximum allowed temperature of  $52^{\circ}\text{C}$  at concentrations  $<200$  ng/mL. There was no obvious change in the mechanical pain detection threshold with increasing concentrations of JNJ-39439335 after single oral dosing of 10 and 50 mg on naïve skin or UVB-sensitized skin.

### 3.5.3. Capsaicin-induced flare

Consistent with the potency of JNJ-39439335 at human TRPV1 receptors ( $\text{IC}_{50} = 4.7$  nM), capsaicin-induced flare intensity was reduced at relatively low plasma concentrations and decreased with increasing JNJ-39439335 concentrations (Fig. 5), although it is difficult to see a correlation of flare area to plasma concentration especially given the high variability of flare area in the absence of JNJ-39439335 and the steep concentration–response relationship. A similar relationship

was observed for flare area. The maximum effect on flare area and flare intensity at 4-hour postdose and 144-hour postdose was observed at concentrations  $\geq 90$  and  $>5$  ng/mL, respectively.

### 3.6. Safety

JNJ-39439335 was well tolerated in oral doses of up to 225 mg. There were no severe adverse events reported, and no participant was withdrawn because of an adverse event. One participant had a serious adverse event (concussion) in part 2 of the study which occurred after the participant was discharged from the study unit and was considered unrelated to study drug by the investigator. Overall, 50 (85%) of 59 participants receiving JNJ-39439335 and 16 (53%) of 30 participants receiving placebo reported at least 1 TEAE (Table 2). The most common TEAEs reported were related to the increases in body temperature. Thermohypoesthesia was reported in 23 (39%) participants receiving JNJ-39439335 in part 1 and 70% participants in part 2, which were generally resolved within 2 to 4 weeks. Only 2 participants in part 2 had thermohypoesthesia that lasted for more than 3 weeks. Of the 89 participants who received JNJ-39439335 or placebo in part 1, 4 participants experienced adverse events of minor or first-degree burns. One participant at the 15-mg dose level (5 days after dose) reported a minor burn manifested as a 1-cm area of erythema on the skin of the hand after removing food from the oven at home after discharge from the study unit. One participant at the 30-mg dose level reported minor burns of the upper gum (on the day of dosing) and lower lip (3 days after dose), possibly associated with the consumption of hot food; this participant also reported a minor burn on his finger when changing a light bulb at home (6 days after dose). Two participants at the highest dose level (225 mg or placebo) experienced minor burns while in the study unit: one participant burned his finger on a hot dinner plate (5 days after dose), and the other accidentally came in contact with a hot food trolley (6 days after dose). A fifth participant reported a burnt feeling on his tongue with no evidence of burn on visual inspection by the investigator (10 mg dose level, 6 days after dose). In part 2, 2 participants at the 50-mg dose experienced minor burns of the mouth associated with consumption of hot food. In addition, 5 participants in part 1 in the 225-mg dose group experienced burning feeling (not physical burn), which was considered as probably related to the study drug by the investigator.

In part 1, the mean maximum body temperature observed across all participants increased with increasing doses (1 to 5 mg range;  $37.6$  to  $38.2^{\circ}\text{C}$ ) and appeared to reach a plateau at 5 mg; the mean maximum body temperatures observed between dose levels of 10 to 225 mg ranged from  $37.9^{\circ}\text{C}$  to  $38.3^{\circ}\text{C}$ . In part 2, the mean maximum body temperature was  $37.2^{\circ}\text{C}$ ,  $37.9^{\circ}\text{C}$ , and  $38.0^{\circ}\text{C}$  after dosing with placebo, 10, and 50 mg, respectively. All increases in body temperature were maximal on the day of dosing and resolved without consequences within 24- to 48-hour postdose. Only 1 participant (part 1, 120-mg JNJ-39439335) had a body temperature  $\geq 39^{\circ}\text{C}$  approximately 11-hour postdose, which was resolved approximately 1 hour later.

Body temperature values slightly increased with increasing JNJ-39439335 concentrations and reached a plateau level at higher concentrations of JNJ-39439335 (Fig. 6A). The relationship between body temperature values and JNJ-39439335 plasma concentrations (according to  $E_{\text{max}}$  model with an initial effect at zero concentration,  $E_0$  where,  $E_{\text{max}}$  is the maximum effect on body temperature; and  $\text{EC}_{50}$  is the plasma concentration of JNJ-39439335 at 50% of the maximum effect)

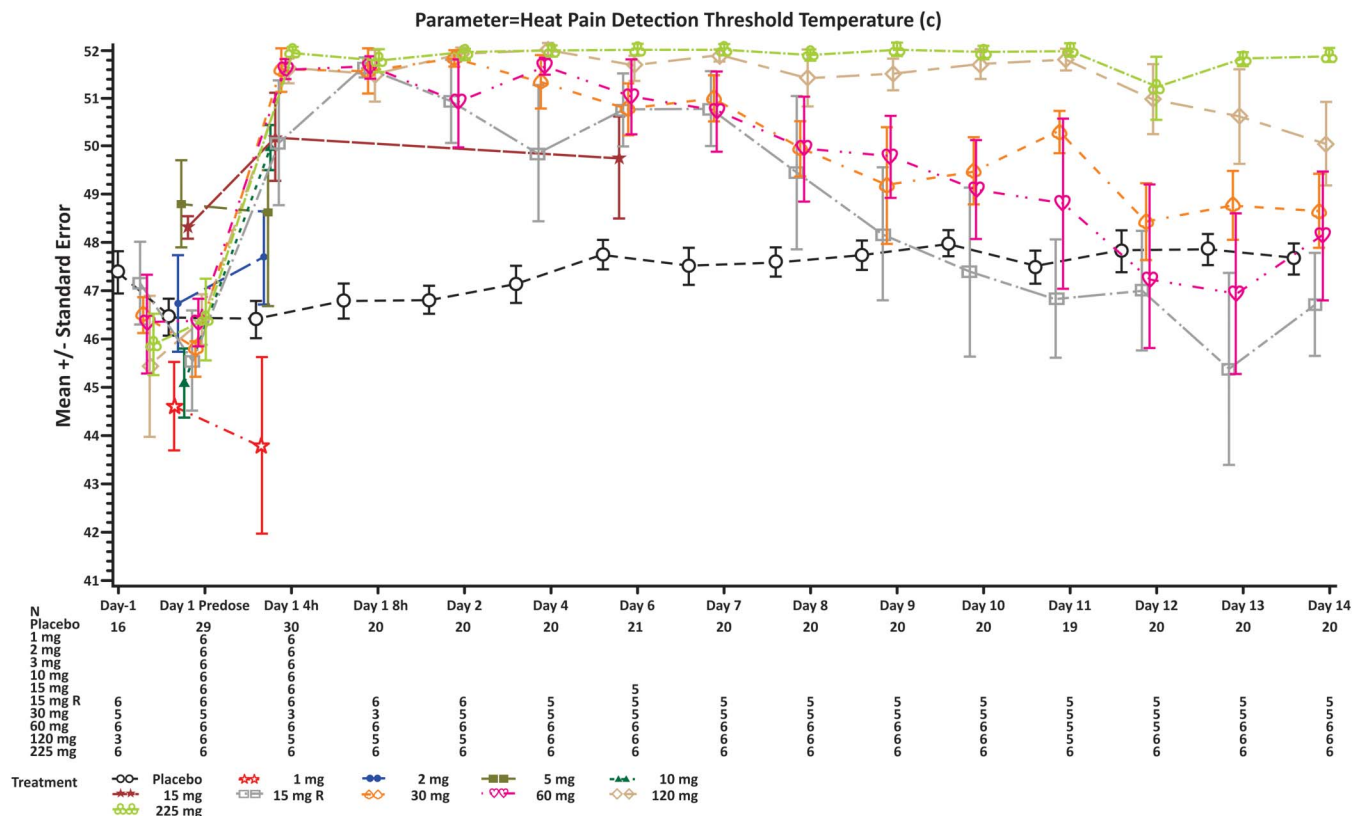


Figure 4. Heat pain detection threshold temperatures after single oral ascending dosing of JNJ-39439335 in healthy men.

demonstrated that the estimated values for  $E_0$ ,  $E_{max}$ , and  $EC_{50}$ , respectively, were 36.6°C, 37.6°C, and 32.7 ng/mL for part 1.

Mean QTcF intervals showed a small decrease after doses of 5 mg and higher, but there was no clear dose-related effect on QTcF observed in either part of the study. Changes in QTcF across individual participants were small and not clinically significant (Fig. 6B). In part 1, QTcF interval shortening of >30 milliseconds vs baseline was observed in 1 participant receiving placebo and 9 participants receiving JNJ-39439335 (10, 120, and 225 mg dose groups:  $n = 2$  each; 15 mg dose group:  $n = 3$ ). No participant had an absolute QTcF interval shortening of >60 milliseconds relative to baseline, or an absolute QTcF value of <330 milliseconds at any postdose time point. In part 2, QTcF interval shortening of >30 milliseconds vs baseline was observed in 4 participants after dosing with JNJ-39439335 50 mg. No participant had an absolute QTcF interval shortening of >60 milliseconds relative to baseline, or an absolute QTcF value of <330 milliseconds at any postdose time point. No participant in either parts of the study showed an increase in QTcF interval of >30 milliseconds vs baseline, or a QTcF interval >450 milliseconds. There were no other consistent or dose-related effects on other safety parameters.

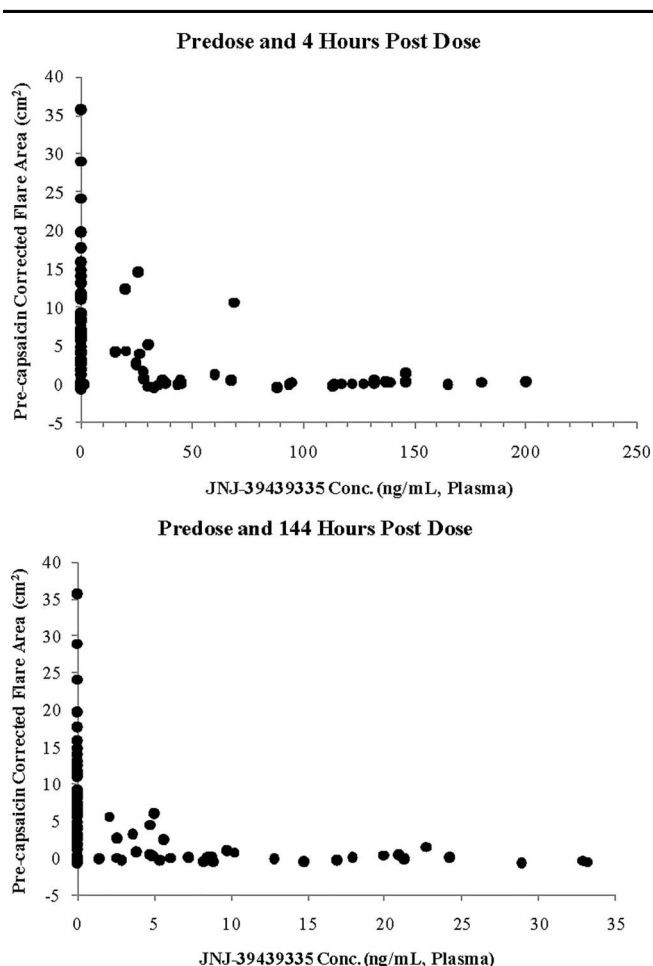
#### 4. Discussion

This was a first-in-human SAD study in healthy men, consisting of 2 parts: part 1 was a single-center, DB, randomized, placebo-controlled, sequential group SAD study that evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of JNJ-39439335 after single oral administration, and part 2 was a DB, randomized, placebo-controlled, 3-way crossover study that evaluated the effect of JNJ-39439335 on

capsaicin-induced flare and sensory testing on naïve and UVB-sensitized skin in healthy men.

In this study, after a single oral administration, JNJ-39439335 was absorbed with median  $t_{max}$  of 2.0 to 4.5 hours across the dose range administered. The highest mean daily exposure ( $AUC_{24h}$ ) observed was 5745 ng·h·mL<sup>-1</sup> after 225 mg JNJ-39439335, which remained well below the corresponding toxic pharmacokinetic parameter at the no-observed-adverse-effect level dose in the most sensitive animal species ( $AUC_{24h} = 10,700$  ng·h·mL<sup>-1</sup> in rat). Because volume of distribution ( $V_dz$ ) generally remains constant with respect to dose, the observed increase in  $CL/F$  and  $V_dz/F$  with increasing doses could be attributable to a decrease in oral bioavailability ( $F$ ) of JNJ-39439335 as doses increase. This observation may be attributed to poor in vivo dissolution of the tablet in the gastrointestinal tract. Because of a small number of participants in this study ( $n = 6$ ) and high intersubject variability of  $C_{max}$  and  $AUC$ , additional data may be needed for dose proportionality evaluation. The mean  $C_{max}$  value (6 ng/mL) obtained from the starting dose of 1 mg in this study was on target and expected to be lower than a near maximally effective plasma concentration from preclinical in vivo studies (ie, 9 ng/mL at the  $ED_{80}$  in the rat carrageenan model of inflammatory pain).

Consistent with findings from other TRPV1 antagonists,<sup>3,4,10</sup> JNJ-39439335 blocked heat-evoked pain in a dose- and concentration-dependent manner, suggesting that these effects are mediated through engagement of the TRPV1 receptor in vivo in humans. The HPD threshold had the greatest utility in characterizing the dose-dependent inhibition of heat pain sensation on both normal and UVB-sensitized skin. The HPT and heat pain latency paradigms used were less useful because



**Figure 5.** Effects of JNJ-39439335 on capsaicin-induced flare after single oral doses (10 and 50 mg) in healthy men.

several participants were able to tolerate the maximum temperature applied in these paradigms at predose.

The topical application of capsaicin to the skin has been performed in numerous clinical studies.<sup>3,8,16</sup> It results in a burning sensation and a neurogenic flare response, characterized by redness and increased local blood flow, which can be quantified using laser Doppler scanning of the affected area.<sup>3</sup> Because capsaicin is suggested to produce this effect through activation of TRPV1 receptors on the local vasculature, blockade of this response by a TRPV1 antagonist such as JNJ-39439335 would suggest *in vivo* pharmacodynamic activity of the compound in humans. In a rat model of capsaicin flare, a single oral dose of 10 mg/kg JNJ-39439335 completely blocked the flare response induced by 1000  $\mu$ g topical capsaicin. JNJ-39439335 dose dependently reduced capsaicin-induced flare in both rats and humans, suggesting this is a useful translational pharmacodynamic model for this class of compounds.

Given the robust blockade of both the HPD threshold and capsaicin-induced flare at the 50-mg oral dose, this was judged to be a reasonable dose for future single-dose proof-of-concept studies with the compound. As TRPV1 is expressed at multiple locations both in the periphery and in the central nervous system (ie, spinal cord and brain), it is possible that the blockade of heat pain and capsaicin-induced flare produced after systemic administration of JNJ-39439335 is mediated at any one or more of these sites; however, the present studies were not designed to make this determination. Also,

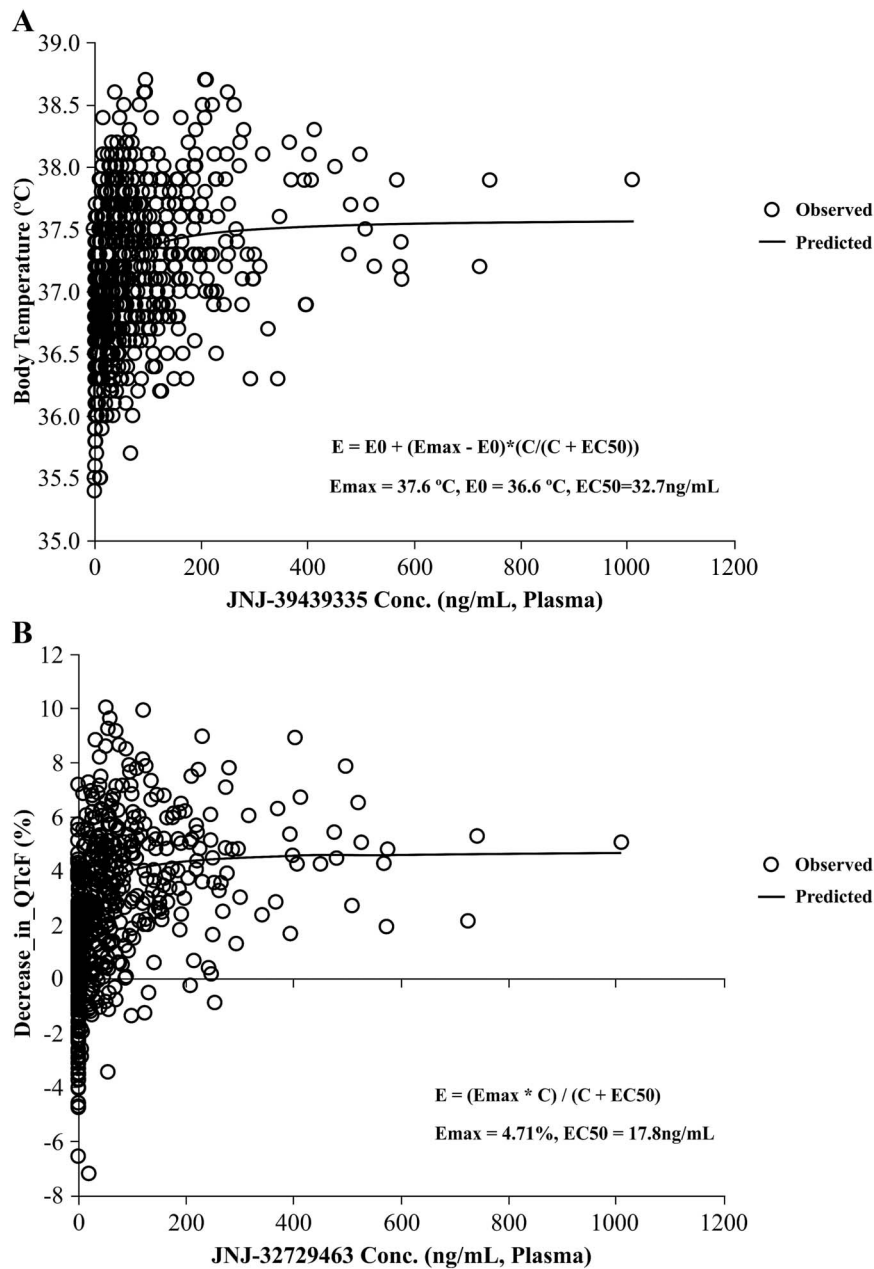
considering that the effects on both these presumably target-related pharmacodynamic responses were sustained at 7 days after dose, the potential for once-weekly dosing of the compound can be considered in multiple-dose studies.

Consistent with its preclinical profile, JNJ-39439335 had no effect on mechanical pain detection threshold testing in healthy human participants. Notwithstanding this finding, as noted earlier, the exact mechanism by which TRPV1 antagonists may have beneficial effects in clinical pain conditions is still unknown. It is also uncertain the extent to which reduction of mechanical pain in healthy participants is relevant to pain reduction in clinical conditions. Consistent with increases in the HPD threshold that were observed during sensory testing at doses of 10 mg and higher, adverse events of decreased heat perception (thermo-hypoesthesia) also occurred at doses of 10 mg and higher. Thermo-hypoesthesia, reported in 23 (39%) participants, generally resolved within 2 to 4 weeks after a single dose of JNJ-39439335. Given the subjective nature of the reported decreases in heat perception and irregular frequency of exposure to sources of heat, it was often difficult for participants to accurately provide a resolution date for thermo-hypoesthesia. Overall, 7 of 79 participants receiving JNJ-39439335 experienced minor or first-degree burns on the hand or the mouth during the study. All these adverse events resolved without clinical consequences. Because these adverse events were observed during the conduct of the study, burn prevention measures were implemented, which included prestudy counseling and provision of temperature-testing devices. Further studies are warranted to evaluate the effectiveness of such measures in preventing thermal burns after exposure to JNJ-39439335. Given the consistency with preclinical studies of JNJ-39439335 and the similarity to the thermo-hypoesthesia described for other TRPV1 antagonists,<sup>4</sup> it is likely that thermo-hypoesthesia is directly related to the mechanism of TRPV1 antagonists including JNJ-39439335 that block activation of the TRPV1 receptor by heat.

Consistent with reports of other TRPV1 antagonists in the literature,<sup>7,12</sup> the most common TEAE observed was increased body temperature after dosing with JNJ-39439335. Body temperature values slightly increased with increasing JNJ-39439335 concentrations and reached a plateau at higher concentrations of JNJ-39439335. All increases in body temperature were maximal on the day of dosing, and resolved without consequences within 24 to 48 hours after dose. The increases in body temperature were well tolerated and in some cases accompanied by participant reporting of feeling hot or cold. Further study is warranted to determine the profile and tolerability of the body temperature changes with multiple dosing of JNJ-39439335.

Consistent with preclinical data that showed decreasing QTc interval with increasing body temperature,<sup>15</sup> QTcF intervals showed a small decrease after dosing with JNJ-39439335. However, these changes in QTcF across individual participants were small and had no clinical sequelae. Future studies will evaluate the relationship between QTcF interval and body temperature with multiple dosing of JNJ-39439335.

Overall, the single-dose safety, pharmacokinetic, and pharmacodynamic profile of JNJ-39439335 demonstrates that it engages and antagonizes TRPV1 in a dose range that is well tolerated; and therefore, the compound is suitable to be evaluated in clinical models of chronic pain, such as osteoarthritis. The safety profile was consistent with that expected based on the pharmacological profile and preclinical testing of the compound, including transient increases in body temperature, decreased heat perception, and small asymptomatic decreases



**Figure 6.** Relationship between JNJ-39439335 plasma concentrations vs oral body temperature (A), and JNJ-39439335 plasma concentrations vs percent decrease in QTcF (B) after single oral ascending dose in healthy participants.

in QTcF interval in some individuals. Although the adverse effects of transiently elevated body temperature and diminished heat perception are consistent with other clinically tested TRPV1 antagonists in the literature and in some cases led to discontinuation of development of those other agents,<sup>3,4,7,10,12</sup> further studies of agents such as JNJ-39439335 are necessary with multiple-dose administration in patients with pain conditions before the benefit-risk profile can be fully evaluated. Therefore, these issues do not yet present a critical problem for the development of JNJ-39439335 because the effective analgesic dose in patients with pain conditions relative to the doses at which these side effects occur is not known, and the potential of patient counseling to manage these adverse effects has not been fully evaluated. A potential advantage of JNJ-39439335 may be more convenient patient dosing (eg, once weekly) given its long pharmacokinetic

half-life, but this possibility will also require further evaluation in multiple-dose studies. If shown to be relatively safe and efficacious in future studies in patients with pain conditions, JNJ-39439335 may provide an alternative treatment option that lacks the potentially serious cardiovascular and gastrointestinal side effects seen with nonsteroidal anti-inflammatory drugs and the respiratory depression seen with opioids.

#### Conflict of interest statement

All authors except M.B. and V.K. are employees of Johnson & Johnson. Drs M.B. and V.K. were employees of Johnson & Johnson at the time of study and are currently employed elsewhere. 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.

The study was funded by Janssen Research & Development (Johnson & Johnson group of companies). The sponsor also provided support for manuscript development.

## Acknowledgements

The authors thank Dr Shruti Shah (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, as well as the investigators for their participation in this study.

## Article history:

Received 14 July 2016

Received in revised form 2 September 2016

Accepted 12 September 2016

## References

- Bolcskei K, Helyes Z, Szabo A, Sandor K, Elekes K, Nemeth J, Almasi R, Pinter E, Petho G, Szolcsanyi J. Investigation of the role of TRPV1 receptors in acute and chronic nociceptive processes using gene-deficient mice. *PAIN* 2005;117:368–76.
- 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.
- 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.
- Crutchlow M, Dong Y, Schulz V, Von Hoydonck P, Laethem T, Maes A, et al. Pharmacologic inhibition of TRPV1 impairs sensation of potentially injurious heat in healthy subjects. Presented at the 110th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, National Harbor, MD, March 18–21, 2009.
- Davis JB, Gray J, Gunthorpe MJ, Hatcher JP, Davey PT, Overend P, Harries MH, Latcham J, Clapham C, Atkinson K, Hughes SA, Rance K, Grau E, Harper AJ, Pugh PL, Rogers DC, Bingham S, Randall A, Sheardown SA. Vanilloid receptor-1 is essential for inflammatory thermal hyperalgesia. *Nature* 2000;405:183–7.
- Flores CM, Vasko MR. The deorphanization of TRPV1 and the emergence of octadecadienoids as a new class of lipid transmitters. *Mol Interventions* 2010;10:137–40.
- Gavva NR, Treanor JJ, Garami A, Fang L, Surapaneni S, Akrami A, Alvarez F, Bak A, Darling M, Gore A, Jang GR, Kessler JP, Ni L, Norman MH, Palluconi G, Rose MJ, Salfi M, Tan E, Romanovsky AA, Banfield C, Davar G. Pharmacological blockade of the vanilloid receptor TRPV1 elicits marked hyperthermia in humans. *PAIN* 2008;136:202–10.
- Helme RD, McKernan S. Neurogenic flare responses following topical application of capsaicin in humans. *Ann Neurol* 1985;18:505–9.
- Honore P, Wismer CT, Mikusa J, Zhu CZ, Zhong C, Gauvin DM, Gomtsyan A, Kouhen REI, Lee CH, 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.
- Karlsten R, Jpnzon B, Quiding H, Carlsson M, Segerdahl M, Malamut R et al. The TRPV1 antagonist AZD1386 inhibits capsaicin and heat evoked pain in healthy volunteers. Presented at the 13th World Congress on Pain, Montreal Canada, August 29–September 2, 2010.
- Keeble J, Russell F, Curtis B, Starr A, Pinter E, Brain SD. Involvement of transient receptor potential vanilloid 1 in the vascular and hyperalgesic components of joint inflammation. *Arthritis Rheum* 2005;52:3248–56.
- Othman AA, Nothhaft W, Awni WM, Dutta S. Effects of the TRPV1 antagonist ABT-102 on body temperature in healthy volunteers: pharmacokinetic/pharmacodynamics analysis of three Phase 1 trials. *Br J Clin Pharmacol* 2013;75:1029–40.
- 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 (Mavatriptan). *J Med Chem* 2015; 58:3859–74.
- 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.
- Van der Linde H, Van Deuren B, Teisman A, Towart R, Gallacher DJ. The effect of changes in core body temperature on the QT interval in beagle dogs: a previously ignored phenomenon, with a method for correction. *Br J Pharmacol* 2008;154:1474–81.
- Van der Schueren BJ, de Hoon JN, Vanmolkot FH, Van Hecken A, Depre M, Kane SA, De Lepeleire I, Sinclair SR. Reproducibility of the capsaicin-induced dermal blood flow response as assessed by laser Doppler perfusion imaging. *Br J Clin Pharmacol* 2007;64:580–90.