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Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Learnings from a Double-Blind, Randomized, Placebo-Controlled, Sequential Group First-in-Human Study of the TRPV1 antagonist, JNJ-38893777, in Healthy Men

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Abstract

Objective: To assess safety, tolerability, pharmacokinetics, and pharmacodynamics of JNJ-38893777, a potent and selective transient receptor potential vanilloid 1 channel antagonist, following ascending single oral administration in healthy men.

Methods: In this single-center, double-blind, placebo-controlled, sequential group, single-ascending-dose phase 1 study, 80 healthy men (18 to 45 years old; body mass index: 18.5 to <30 kg/m^2) were randomized to receive either JNJ-38893777 (n=6) or placebo (n=2) per group (total 10 groups) in a dose-escalation manner. In part 1, an early tablet formulation was administered under fasting conditions at 5, 15, 45, 125, 250, or 500 mg. In part 2, a new tablet formulation was administered at 250 mg (fasted), 250 (fed, high-fat), 375 (fed, high-fat), or 500 mg (fed, high-fat). Serial blood and urine samples were collected over 120 hours post-dose.

Results: JNJ-38893777 concentrations peaked from 3.0 to 5.5 hours (median) after oral administration, and then declined multi-exponentially with a prolonged terminal phase. Renal clearance of JNJ-3889377 was negligible. The C_{max} and AUC_{∞} of the early formulation increased with increasing doses but less than dose-proportionally over 5-500 mg (fasted) doses. No improvement in exposure was observed with the new tablet formulation (250 mg) under fasting condition. However, high-fat meal substantially increased exposure of JNJ-38893777 by 11- to 22-fold and reduced inter-individual variability from 73-85% to 23-24%. Adverse events were predominately mild to moderate in severity with no evidence of exposure dependence up to 500 mg (fed). No meaningful concentration-related increases in body temperature or QTcF were observed. A significant increase ($P<0.05$) in heat pain detection threshold (~3 °C) was observed at 250-500 mg (fed).

Conclusion: JNJ-38893777 was tolerated at single doses up to 500 mg (fed) and is suitable for further clinical development.

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ABBREVIATIONS

ANCOVA: Analysis of Covariance; AUC: Area Under the Curve; BMI: Body Mass Index; C: Celcius; CFA: Complete Freund's Adjuvant; CV: Coefficient of Variation; DLT: Dose-Limiting Toxicity; ECG: Electrocardiogram; LC-MS/MS: Liquid Chromatography/Mass Spectrometry/ Mass Spectrometry; MABEL: Minimum Anticipated Biological Effect Level; MRSD: Maximum Recommended Starting Dose; MRT: Mean Residence Time; MTD: Maximum Tolerated Dose; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; NOAEL: No Observed Adverse Effect Level; TEAE: Treatment-Emergent Adverse Event; TRPV1: Transient Receptor Potential Vanilloid 1

INTRODUCTION

Both nociceptive and neuropathic pain cause suffering and disability in many patients, and hence are important health concerns. It is estimated that approximately 170 million people worldwide suffer from nociceptive pain, while around 38 million people have neuropathic pain [1]. Currently, available treatment options for nociceptive pain include opioids and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), while opioids, anticonvulsants (gabapentin) and antidepressants (duloxetine) are used for treating neuropathic pain [2]. However, there are still concerns about the safety (e.g., gastrointestinal ulcers and cardiovascular effects with NSAIDs) and tolerability (e.g., dependence and abuse potential, respiratory depression and cognitive dampening effects with opioids) of these drugs. In addition, neuropathic pain is often undertreated. Undertreated pain can impair an individual's ability to carry out daily activities and diminish quality of life. It has been shown that undertreated pain has significant physical, psychological, and financial consequences [3].

Analgesic compounds with novel mechanisms of action have the potential to be valuable alternatives to currently used therapies. One such novel mechanism involves blocking of the transient receptor potential vanilloid 1 (TRPV1), a calcium-permeable ion channel activated during inflammation in small-diameter neurons innervating the skin and viscera [4]. TRPV1 is activated by vanilloid-containing compounds such as capsaicin, as well as heat, acid, endogenous pro-inflammatory mediators and ethanol [5]. TRPV1 expression is most prevalent in small-diameter neurons that give rise to C-polymodal nociceptors innervating the skin and viscera including the colon, oesophagus, stomach, pancreas, bladder, and uterus. TRPV1 is also expressed on vagal afferents innervating the airway walls at the level of the trachea and bronchi. In addition to being activated by a range of inflammatory mediators, TRPV1 expression also increases in a variety of inflammatory conditions [4,6-8]. This increased expression may underlie some of the pain and irritation associated with certain diseases with an inflammatory component. Evidence from experiments with TRPV1 knock-out mice and TRPV1 antagonists provides support for an important role of the TRPV1 receptor in pain and inflammatory sensory sensitization [9-14].

JNJ-38893777 [2-(1-piperidinyl)-*N*-[4-(trifluoromethyl) phenyl]-7-[3-(trifluoromethyl)-2-pyridinyl]-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*d*]azepin-4-amine sulfate] is a potent, selective, competitive antagonist of the TRPV1 channel under consideration for development for the treatment of pain. Preclinical studies with JNJ-38893777 have demonstrated analgesic activity in established animal models of hyperalgesia, including carrageenan- evoked thermal hyperalgesia and Complete Freund's Adjuvant (CFA)-evoked thermal hyperalgesia. JNJ-38893777 is also shown to normalize the pain behaviors evoked by distension of the acid-sensitized rat colon. In addition, JNJ-38893777 blocked capsaicin induced hypotension and hypothermia in a concentration/dose dependent manner. The compound had acceptable pharmacokinetic properties across animal species and also demonstrated acceptable safety margins in both rat and dog 4-week toxicology studies (unpublished internal data). Preclinical pharmacology studies in conscious dogs indicate that JNJ-38893777 is associated with shortening of the QT interval. Therefore QT changes were assessed in this study by frequent 12-lead Electrocardiogram (ECG) monitoring during the predicted time of pharmacologically active plasma concentrations of JNJ-38893777. Additionally, JNJ-38893777 increased core body temperature by up to 1°C and inhibited capsaicin-induced hypothermia in rats at oral doses of 3 – 30 mg/kg. In a five-day, once daily, repeat dose study, it was found that the ability of JNJ-38893777 to increase core temperature was attenuated, suggesting that tolerance may develop to this effect over time (unpublished data).

The current first-in-human study with JNJ-38893777 was conducted to explore safety, tolerability, and pharmacokinetics at wide dose range to define the margin between the potentially therapeutic dose and that associated with dose-limiting toxicity (DLT). Two early solid dosage formulations were used and the food effect on the pharmacokinetics of JNJ-38893777 was evaluated. The pharmacodynamic activity of JNJ-38893777 was also evaluated based on oral body temperature, ECG parameters, heat pain detection threshold, and heat pain tolerance.

MATERIALS AND METHODS

Study population

Healthy, non-smoking men aged 18 to 45 years (inclusive), body mass index (BMI) of 18.5 to <30 kg/m^2 (inclusive), and with no history and current evidence of any significant medical illness, laboratory abnormalities, or investigational findings were enrolled. All participants were nonsmokers for at least 6 months prior to study drug administration. Participants with oral temperature greater than 37.5ºC at screening or day –1 were excluded from the study. Participants were prohibited from any form of strenuous exercise, alcohol consumption, and smoking during the study. Consumption of food and beverages containing methylxanthine and quinine was prohibited from 48 hours before dosing to 72 hours postdose, while consumption of grapefruit, grapefruit juice and/or Seville oranges was prohibited from 7 days before and for 7 days following study drug administration.

Use of any prescription, over-the-counter (including NSAIDs) or herbal medication (including herbal tea or garlic extract), vitamins or mineral supplements was prohibited within 14 days prior to study drug administration and during the study. St. John's Wort was prohibited within 30 days of study drug administration and during the study. Paracetamol (acetaminophen) was not permitted at any time.

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.

Study design

This was a single-center, double-blind, randomized, placebo-controlled, sequential group, single ascending dose study to evaluate safety, tolerability, and pharmacokinetics of JNJ-38893777 in healthy male participants in 2 parts (Part 1 and Part 2).

In Part 1, 48 healthy men were enrolled in 6 cohorts. In each cohort, participants were randomly assigned to JNJ-38893777 (n=6) or placebo (n=2). The planned JNJ-38893777 doses were 5, 15, 45, 125, 250, and 500 mg, after an overnight fast. If DLT was reached, it was planned to reduce the dose to an intermediate dose to determine the maximum tolerated dose (MTD). In case the MTD was not reached in these 6 planned cohorts, the sponsor had the option to add cohorts (n=8, 6 active, 2 placebo) to the study until the MTD was achieved. To ensure acceptable tolerability for each cohort, 2 participants were dosed initially on day 1 (1 with JNJ-38893777 and 1 with placebo). After 48 hours postdose assessments of these 2 participants, the remaining 6 participants were dosed.

In Part 2, a new tablet formulation of JNJ-38893777 with precipitation inhibitor was used. Up to 32 healthy men were planned to be enrolled in up to 4 cohorts with JNJ-38893777 doses of 250 (fasted), 250 (fed), 375 (fed) and 500 (fed) mg. In each cohort, 8 participants were randomly assigned to either JNJ-38893777 (n=6) or placebo (n=2). The planned JNJ-38893777 dose level was 250 mg administered under fasting (cohort 1) and fed (high-fat meal) condition (cohort 2). Based on results from cohorts 1 and 2, it was found that administration of the 250 mg dose with a high-fat meal was associated with higher mean C_{max} and AUC_{24h} compared with the values in the fasted state. As a result, dose escalation was progressed in the fed state to determine the MTD.

For both Parts 1 and 2, participants were screened within 28 days prior to 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.

Starting dose selection

The starting dose for this first-in-human study was critical and was carefully selected based on available data from preclinical studies. The safe starting dose was estimated and selected according to the Food and Drug Administration (FDA) guidance on estimating the Maximum Recommended Starting Dose (MRSD) [15], the Minimum Anticipated Biological Effect Level (MABEL) principle according to the updated European Medicines Agency guidance [16], and nonclinical pharmacokinetic and pharmacodynamic data for JNJ-38893777. Allometric scaling [17] was used to predict clearance and volume of distribution in humans and calculate exposure based on the predicted pharmacokinetic parameters and assumptions regarding bioavailability.

Based on the no observed adverse effect levels (NOAEL) in rats and dogs during 4-week toxicity studies (unpublished data), the MRSD for this trial was calculated to be 18 mg/m^2/day (0.49 mg/kg/day); therefore, for a person with a body weight of 70 kg, the MRSD is 34 mg/day. However, additional consideration was given to the appropriateness of the first starting dose of JNJ-38893777 based on the MABEL and hence, a starting dose of 5 mg was selected which was substantially lower than the calculated MRSD of 34 mg. This starting dose of 5 mg was predicted to result in plasma concentrations (17-66 ng/mL) that are lower than the minimal effective concentrations observed in relevant preclinical in vivo assays (177 - 1073 ng/mL, unpublished observation).

Dosage and administration

In this study, early simple tablet formulations were used. In Part 1, JNJ-38893777 was supplied as free-base equivalent of 5 mg, 25 mg, and 250 mg tablets. In Part 2, JNJ-38893777 was supplied as free-base equivalent of 25 mg and 250 mg tablets. In addition to JNJ-38893777, the compositions of the tablets used in Part 1 and Part 2 were slightly different. The early tablet in Part 1 contained microcrystalline cellulose (filler), lactose (filler), sodium starch glycolate (disintegrant), magnesium stearate (lubricant), and colloidal silica (flow agent). The tablet used in Part 2 contained microcrystalline cellulose (filler), lactose (filler), sodium starch glycolate (disintergrant), magnesium stearate (lubricant) and hydroxypropyl methylcellulose (binder). Placebo tablets of matching color and size were used.

In Part 1, JNJ-38893777 or placebo was administered orally after an overnight fast (at least 10 hours) with 240 mL of water to participants in a sitting position and remaining in a semi-recumbent position for 4 hours postdose. Free access to drinking water was allowed until 2 hours prior to dosing and from 2 hours post dosing. Water and other fluids (methylxanthine-free) were allowed *ad libitum* throughout the rest of the study.

In Part 2, JNJ-38893777 was administered under fasting condition, as described earlier, in cohort 1 (250 mg), and was administered under fed (high-fat meal) condition in cohorts 2 (250 mg), 3 (375 mg), and 4 (500 mg). Under fed condition, JNJ-38893777 was administered immediately after consuming (over 30 minutes) a typical high fat breakfast on day 1. No food was allowed for 4 hours post-dose. Lunch and dinner were consumed approximately 4 and 10 hours, respectively, after dosing.

Dose escalation criteria

The decision to progress to the next higher dose was based on adequate review of blinded interim safety data, oral temperature, and pharmacokinetic data up to 24 hours postdose. Each subsequent dose administration was performed if, and only if, the investigator and the sponsor safety physician found the results of the safety analyses of the preceding dose administration satisfactory. Dosing of consecutive cohorts was separated by a minimum of one week.

The highest dose administered in this study did not to exceed the exposure associated with the NOAEL in rat (28,300 ng. h/mL,

data on file, Janssen Pharmaceutical Research and Development LLC., Raritan, NJ, USA).-

PHARMACOKINETIC ASSESSMENTS

Sample collection and handling

Venous blood samples were collected at predose, and at 30 minutes, 1-, 1.5-, 2-, 3-, 4-, 5-, 6-, 8-, 10-, 12-, 16-, 24-, 36-, 48-, 72-, 96-, and 120-hours relative to study drug dose on day 1 for the determination of JNJ-38893777 concentrations. The blood samples were cool centrifuged (10 minutes at 1300 rpm) and the obtained plasma was stored at ≤−20ºC. Urine samples were collected at the following intervals relative to dosing −18 to −14 hours (predose), 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 postdose. Total volume of the urine sample over each time interval was recorded. A 10-mL aliquot in each interval was collected and stored at ≤−20ºC until shipped to the analytical facility.

Sample analytical method

Plasma concentrations of JNJ-38893777 were determined by a validated liquid chromatography with tandem mass spectrometry detection (LC-MS/MS) method. Urine concentrations of JNJ-38893777 were determined using a research qualified LC-MS/MS method. After addition of the stable isotope labeled internal standard and protein precipitation with acetonitrile, 10 µl of the resulting supernatant was injected onto a 3 cm x 4.6 mm I.D. column, packed with 3.5 µm XBridge C18 (Waters, Milford, MA, USA) using an Agilent 1100 liquid chromatograph (Santa Clara, CA, USA) and Shimadzu SIL-HTc autosampler (Kyoto, Japan). The mobile phase consisted of 31% Formic acid (0.1% in water) and 69% methanol at a flow rate of 1.5 mL/min. This chromatography system was coupled to a Triple Quadrupole Mass Spectrometer API-3000 (AB Sciex, Framingham, MA, USA), with Turbo-Ionspray™ Interface used in the positive ion-mode. The lower limit of quantitation was 1.00 ng/mL and the analytical range was 1.00 to 1000 ng/mL for both plasma and urine, with a precision (expressed as percentage of coefficient of variation [%CV]) within 5.9% and accuracy (expressed as percent bias) of -5.0% to 2.3% for plasma and a precision of within 4.7% and accuracy of -14.6 to -19.0% for urine.

Pharmacokinetic analyses

Plasma and urine drug concentrations were subjected to pharmacokinetic analysis using non-compartmental methods by WinNonlin Enterprise Version 5.2.1 (Pharsight Corporation, Mountain View, California, USA) and EXCEL 2007 (Microsoft Corporation). Area under the plasma concentration-time curve (AUC) was estimated by linear trapezoidal rule. The following pharmacokinetic parameters of JNJ-38893777 were estimated for each participant at each dose level: maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration (AUC_{last}), area under the concentration versus time curve from time zero to infinity (AUC_{∞}, calculated as $AUC_{\infty} = AUC_{last} + C_{last}/\lambda_z$ where C_{last} is the last observed quantifiable concentration, and λ_z is the terminal elimination rate constant), elimination half-life associated with the terminal slope (λ_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 dose/AUC_{∞}), apparent volume of distribution after extravascular administration (Vd_z/F, calculated as $Vd_z/F = D/(\lambda_z * AUC_{\infty})$, and mean residence time (MRT, calculated as AUMC/AUC). Additionally, cumulative amount of unchanged drug excreted into the urine (A_e) calculated by multiplying the urinary volume with urinary concentration, A_e as a percent of dose (% A_e) calculated as (A_e/Dose)*100, and renal clearance (CL_R) calculated as a ratio of Ae to AUC were estimated.

HEAT PAIN THRESHOLD AND TOLERANCE ASSESSMENTS

In Part 2, the effect of JNJ-38893777 on the heat pain detection threshold and heat pain tolerance was assessed for each dose level at baseline and at approximately 4 hour post dose (t_{max} observed from Part 1) on the forearm of participants. A computer-controlled 9x9 mm Peltier device (MSA Thermotest, Somedic, Sweden) was positioned on the volar aspect of the forearm, approximately 17 cm from the wrist crease and within approximately 1 cm of the midline. The baseline temperature of the probe was 32ºC. For threshold measurements, the temperature was gradually increased at a rate of 1ºC/second. The test was stopped and the temperature threshold returned to baseline by the participant pushing a button on a response unit when the heat pain threshold (first sensation of heat pain) was reached. This was repeated three times and the average value recorded. The procedure for heat pain tolerance was identical except that participants were instructed to push the button when they felt the maximum tolerable pain. The cut-off temperature for either test was 52ºC in order to prevent skin injury.

Safety assessments

Safety evaluations included reporting of treatment-emergent adverse events (TEAEs), clinical laboratory testing, ECG, physical examination, neurological examination and monitoring of vital signs and oral temperature from predose to postdose time points.

Triplicate 12-lead ECGs were performed at screening; on day 1, within 30 minutes (predose), and at 1, 2, 3, 4, 5, 6, 8, and 12 hours postdose; on day 2 at 24 hours postdose; on day 3 at 48 hours postdose; and at follow-up visit. Continuous lead-II ECG monitoring was conducted from −1 hour (predose) to 12 hours postdose on day 1.

Oral temperature was taken at screening, on day −1 at T+1 hours, T+2 hours, T+3 hours, T+4 hours, T+5 hours, T+6 hours, T+7 hours, T+8 hours, T+10 hours, T+12 hours, and T+16 hours (where T is the planned study drug dose time on day 1); and within 1 hour prior to study drug dose on day 1, and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 30, 36, 48, 72, 96, and 120 hours postdose, and at the follow-up visit. Participants refrained from drinking hot or cold fluids within 30 minutes before each oral temperature measurement.

Statistical analysis

No formal statistical calculations of sample size were conducted. A sample size of 8 participants per group was considered sufficient to allow clinical judgment of safety and tolerability as well as pharmacokinetic assessments for this first clinical study. All participants receiving at least one dose

of JNJ-38893777 were included for pharmacokinetic analyses while all participants receiving one or more doses of JNJ-38893777 or placebo were included for pharmacodynamics and safety analyses. Safety data were summarized descriptively. Pharmacokinetic parameters of JNJ-38893777 were summarized and descriptive statistics (means, median, standard deviations and %CV) were generated for each dose group. The graphical assessment of dose proportionality was performed for AUC and C_{max}.

The heat pain detection threshold and heat pain tolerance were evaluated at baseline and following treatment using analysis of covariance (ANCOVA) model. Comparisons between the on-treatment heat pain detection threshold and heat pain tolerance (temperature in degrees Celsius) of active versus placebo were made. The analysis of heat pain detection threshold and heat pain tolerance data was exploratory. The baseline heat pain detection threshold and heat pain tolerance were used as a covariate in each model, respectively.

Pharmacokinetic/pharmacodynamic analyses

The relationship between plasma concentrations and corresponding pharmacodynamic measurements (core body temperatures and QTcF) were plotted. The E_{max} model was applied to describe the exposure-effect relationship, where E_{max} was the maximum effect and EC_{50} was the plasma concentration of JNJ-38893777 at 50% of E_{max}.

RESULTS

Demographics and baseline characteristics

The study was conducted from 4th April 2008 to 15th January 2009. A total of 80 healthy men were randomized into 10 treatment groups and completed the study (Part 1: original tablet formulation, fasted, n=36 for JNJ-3889377, and n=12 for placebo; Part 2: new tablet formulation, n=24 for JNJ-3889377, and n=8 for placebo). Consistent with inclusion and exclusion criteria, the demographic and baseline characteristics of participants were comparable across all the cohorts and between treatments. Of the 80 men, the majority were white (75%) with age of 18 to 45 years, and BMI of 18.7 to 29.4 kg/m^2.

Pharmacokinetic results

In Part 1, a single dose of JNJ-38893777 (early tablet formulation) was administered under fasted condition. Due to poor bioavailability and high variability in C_{max} and AUC observed, a new tablet formulation with precipitation inhibitor added was developed and used in Part 2 under either fasted or fed conditions. Renal excretion of JNJ-38893777 was negligible. All urine concentrations were below the limit of quantification. Percentage of the dose excreted in the urine unchanged and renal clearance could not be estimated. The results indicated that JNJ-38893777 was mainly eliminated via non-renal clearance.

Part 1

Following oral administration as a tablet formulation under fasting conditions, JNJ-38893777 was absorbed with a median t_{max} of 3.99 to 5.01 hours. The concentrations then declined multi-exponentially with mean elimination half-life of 5.5 to 29.5 hours over doses of 5 to 500 mg (Table 1 and Figure 1). All participants receiving JNJ-38893777 showed systemic exposure (C_{max} and AUC) to JNJ-38893777, and the exposure increased with increasing doses (Figure 1). Dose-normalized C_{max} and dose-normalized AUC_{∞} decreased with increasing doses (Figure 2), indicating less than dose proportional increase in exposure over doses of 5 to 500 mg. Additionally, the exposure was highly variable with %CV up to 166% (Table 1).

The values for CL/F and Vd_z/F seemed to increase with increasing dose levels (Table 1). Since the volume of distribution (Vd_z) generally remains constant with respect to dose, the observed increase in CL/F and Vd_z/F with increasing doses may have been due to a decrease in oral bioavailability (F) of JNJ-38893777 as doses increased. This observation may be due to poor in vivo dissolution of the tablet in the gastrointestinal tract.

Part 2

In Part 2, a New Tablet Formulation (NF) with a precipitation inhibitor (hydroxypropyl methylcellulose) was used. For the initial dose of 250 mg, JNJ-38893777 was administered under fasted and fed conditions to evaluate food effect. Based on the results obtained, all subsequent doses were administered under

Table 1: Mean (%CV) Pharmacokinetic Parameters for JNJ-38893777 Following Single Oral Administration of an Early Tablet Formulation under Fasted Conditions to Healthy Men, Part 1 (N=6/Dose).

Treatment	C_{max} (ng/mL)	[1]t_{max} (h)	AUC_{∞} (h.ng/mL)	CL/F (L/h)	Vd_z/F (L)	$t_{1/2}$ (h)	MRT (h)
5 mg	20.2 (77.6)	4.48 (3.00-5.02)	130 (98.2)	71.7 (74.0)	405 (46.3)	5.5 (55.5)	8.7 (39.5)
15 mg	52.2 (79.0)	4.49 (1.98-5.07)	340 (66.7)	56.5 (43.6)	755 (31.0)	10.1 (26.5)	10.5 (18.5)
45 mg	74.9 (86.8)	5.00 (3.95-5.00)	465 (57.0)	116 (39.8)	2301 (44.2)	13.8 (26.6)	13.0 (10.7)
125 mg	154 (53.8)	3.99 (2.97-5.00)	911 (20.7)	142 (21.0)	3866 (44.5)	18.1 (27.3)	15.2 (20.1)
250 mg	357 (166.2)	3.99 (2.98-5.00)	1577 (99.2)	245 (50.4)	8186 (40.7)	29.5 (64.4)	20.3 (13.1)
500 mg	792 (112.4)	5.01 (4.98-6.05)	5159 (102.2)	212 (87.2)	7104 (75.7)	28.3 (37.7)	19.4 (14.1)

[1]Data represented as median (minimum, maximum) %CV: percentage of coefficient of variation; AUC: area under the curve; MRT: maximum tolerated dose.

fed conditions. Mean (%CV) PK parameters are summarized in Table 2.

Effect of formulation on the bioavailability of JNJ-38893777 under fasted condition: Results from the new tablet formulation were compared with those from the early tablet formulation (250 mg under fasted condition). The results showed that adding a precipitation inhibitor to the new tablet formulation did not improve bioavailability of JNJ-38893777 (under fasting conditions). Mean C_{max} and AUC_{∞} values from the new tablet formulation were less than those from the early formulation (Table 1, Table 2, and Figure 3a). However, the variability in C_{max} and AUC values for the new tablet formulation was less than those for the original formulation.

Food effect on the bioavailability of JNJ-38893777 new tablet formulation: A high-fat meal substantially increased the bioavailability of JNJ-38893777 from the new tablet formulation. Mean C_{max} and AUC_{∞} values under fed condition, relative to fasted condition, increased by 22-fold and 11-fold, respectively. In addition, inter-individual variability was substantially reduced by high-fat meal from 85% to 24% for C_{max}, and from 73% to 23% for AUC_{∞} (Table 2 and Figure 3b). With high fat meal, mean $t_{1/2}$ was extended from 23.3 hour to 51.2 hour.

Pharmacokinetics of JNJ-38893777 following single ascending doses of a new tablet formulation under fed condition: Mean (%CV) pharmacokinetic parameters of JNJ-38893777 from the new formulation under fed condition are summarized in Table 2, and plasma concentration-time profiles are shown in Figure 4. Consistent with the early tablet formulation, JNJ-38893777 was absorbed from the new tablet formulation with median t_{max} of 4.98 to 5.50 hours, following which the concentrations declined multi-exponentially (Figure 4). Under fed conditions with the new formulation, a 5-9 fold increase in C_{max} and AUC_{∞}, relative to those for the original formulation under fasting conditions was observed (Table 1 and Table 2). Dose-normalized AUC_{∞} values were consistent across doses of 250 to 500 mg, indicating dose proportional increase in overall exposure (Figure 5). This was confirmed by the finding that mean values for CL/F and Vd_z/F remained relatively consistent across doses (Table 2). Under fed condition, mean elimination half-life ranged from 33.7 hours to 51.2 hours over doses of 250 to 500 mg (Table 2).

Effect on heat pain detection threshold results

Consistent with the mechanism of action of JNJ-38893777 as a TRPV1 receptor antagonist, higher exposure of JNJ-38893777 during fed condition at 250-500 mg resulted in a statistically significant increases ($P<0.05$) in both heat pain detection threshold (approximately 3.2 to 3.6 ºC) and heat pain tolerance limit (0.6-0.8 ºC), compared to placebo.

Pharmacokinetic-pharmacodynamic relationship

Core body temperature: The relationship between JNJ-38893777 plasma concentrations and core body temperature was evaluated and illustrated graphically in Figure 6a. No meaningful concentration-related increases in body temperature were observed. No increase in body temperature above 38.5°C was observed for JNJ-3889377 concentrations up to 6000 ng/mL. Small initial increases were observed which then quickly reached a plateau level as JNJ-38893777 concentrations increased (Figure 6a).

QTcF: No apparent relationship between QTcF and JNJ-38893777 plasma concentrations was observed. JNJ-38893777 concentrations up to approximately 6000 ng/mL did not lead to a decrease or increase in QTcF below 340 msec or above 450 msec, respectively. Only minor decreases in QTcF from baseline were observed in some participants, and thus, individual decreases in QTcF values on day 1 relative to the predose value on the same

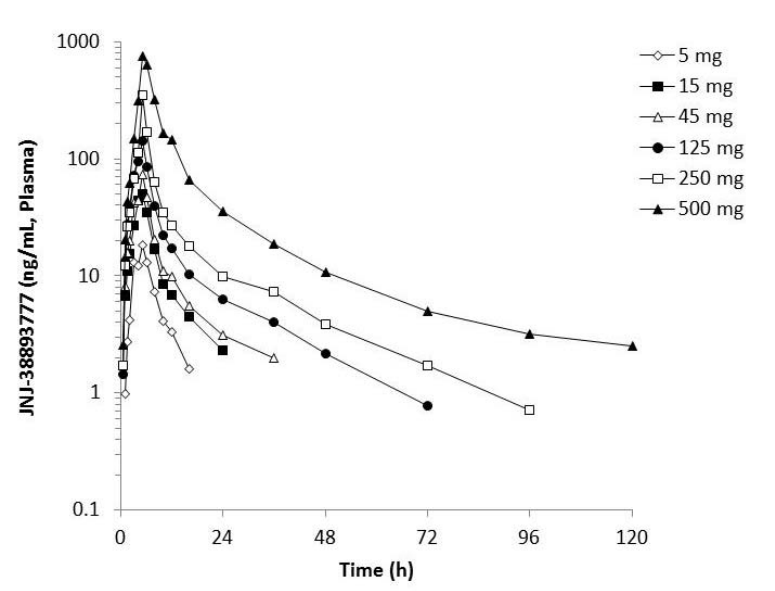

Figure 1 Mean (SD) Plasma Concentrations-Time Profiles of JNJ-38893777 Following Single Oral Administration to Healthy Men under Fasted Conditions of an Early Tablet Formulation in Part 1.

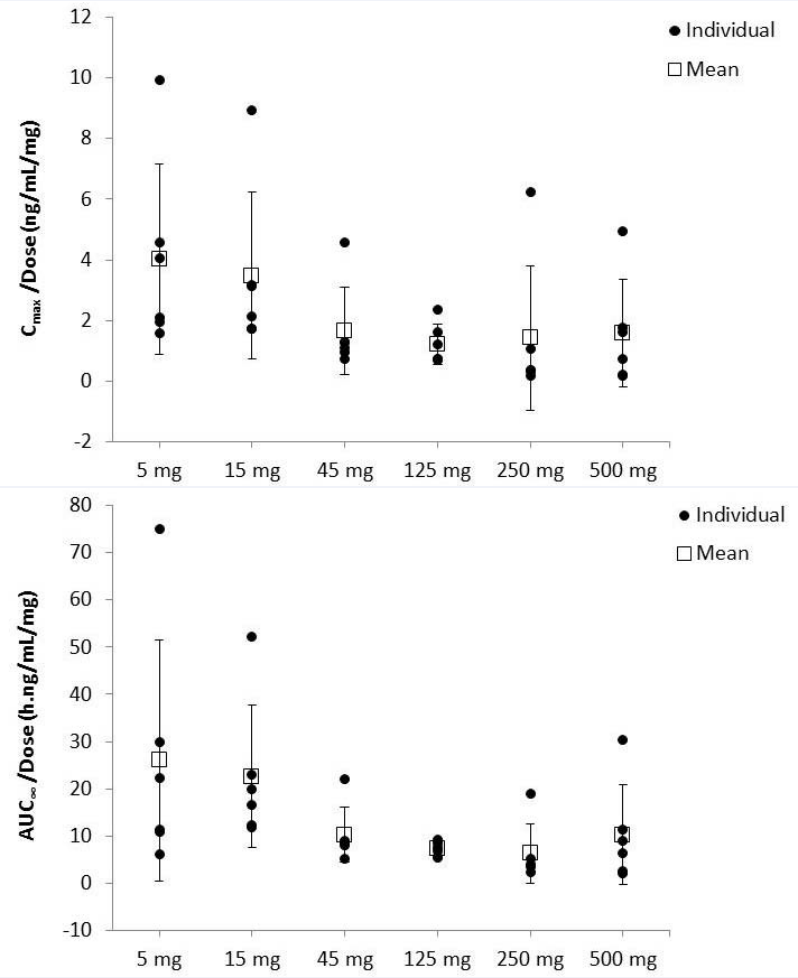

Figure 2 Relationship Between Dose Normalized C_{max} and Dose Normalized AUC_{∞} Versus JNJ-38893777 Doses Following Single Oral Administration of an Early Tablet Formulation under Fasted Condition in Part 1.

Table 2: Mean (%CV) Pharmacokinetic Parameters for JNJ-38893777 Following Single Oral Administration of the New Tablet Formulation (NF) under Fasted or Fed Conditions to Healthy Men, Part 2 (N=6/Dose).

Treatment	C_{max} (ng/mL)	[1]t_{max} (h)	AUC_{∞} (h.ng/mL)	CL/F (L/h)	Vd_z/F (L)	$t_{1/2}$ (h)	MRT (h)
250 mg NF fasted	144 (84.8)	3.02 (2.97-6.00)	1288 (72.5)	385 (109.4)	8981 (66.6)	23.3 (56.9)	20.2 (27.2)
250 mg NF fed	3202 (24.4)	4.98 (2.00-6.07)	14569 (23.0)	17.9 (22.3)	1410 (67.0)	51.2 (50.4)	18.2 (19.6)
375 mg NF fed	2998 (16.0)	4.99 (2.97-5.93)	23807 (22.5)	16.6 (28.0)	783 (41.7)	33.7 (44.6)	19.4 (11.1)
500 mg NF fed	4728 (24.8)	5.50 (2.92-6.00)	30735 (41.0)	19.1 (47.5)	1260 (70.0)	43.6 (50.4)	23.1 (27.2)

NF=New Formulation; [1]Data represented as median (minimum, maximum) %CV: Percentage of Coefficient of Variation; AUC: Area under the Curve; MRT: Maximum Tolerated Dose

day were calculated and plotted against JNJ-38893777 plasma concentrations (Figure 6b). Decreases in QTcF values were less than 10% at any measured concentration and no increases greater than 8% were observed (Figure 6b).

Safety: There were no deaths, serious TEAEs, or discontinuations due to TEAEs reported. Overall, 51 participants (64%) (JNJ-38893777: n=42, 70%; placebo: n=9, 45%) experienced ≥1 TEAE. The most common TEAEs (observed in ≥5% participants) included pyrexia (19%), headache (11%), feeling cold (9%), parasthesia (9%), hypoesthesia (8%), dizziness (8%), and feeling hot (6%) (Table 3). Pyrexia was observed only in the JNJ-38893777 treatment groups with maximum incidence seen in participants in Part 2 receiving JNJ-38893777 in the fed state. All incidences of hypoesthesia (8%) characterized by decreased heat perception were reported in participants in Part 2 receiving JNJ-38893777 in the fed state. All the adverse events

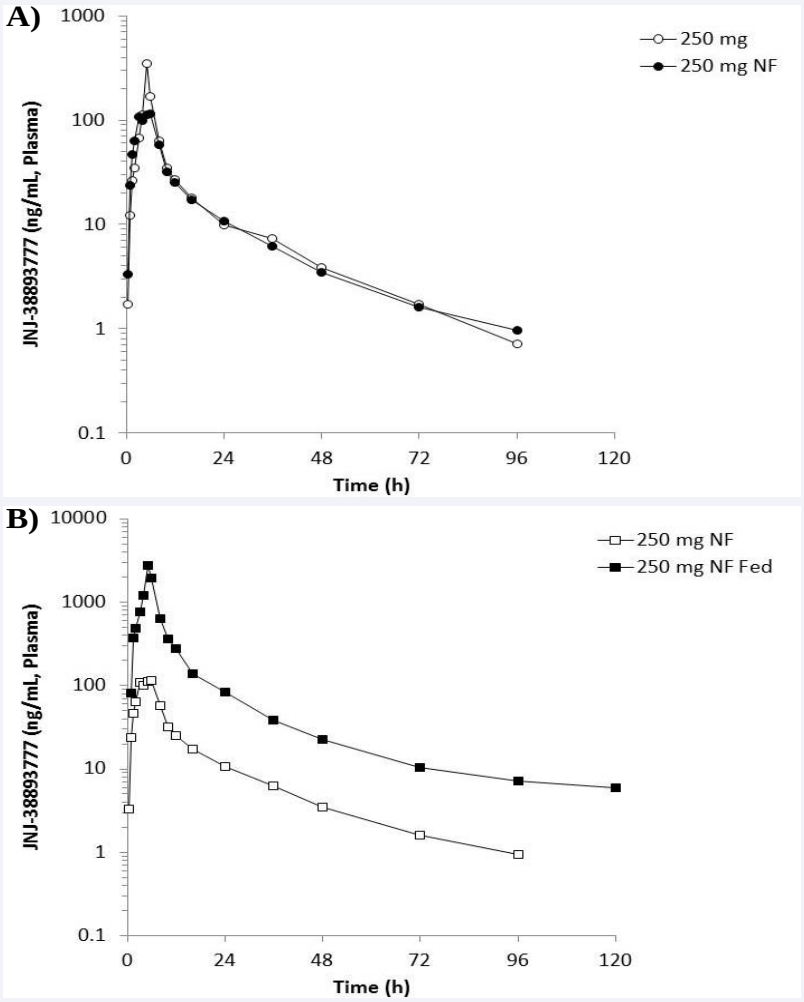

Figure 3 Mean (SD) Plasma Concentration-Time Profiles of JNJ-38893777 (250 mg) Administered Orally (A) Under Fasted Conditions of an Early Tablet Formulation and a New Tablet Formulation (NF), and (B) New Tablet Formulation (NF) Under Fasted and Fed Conditions.

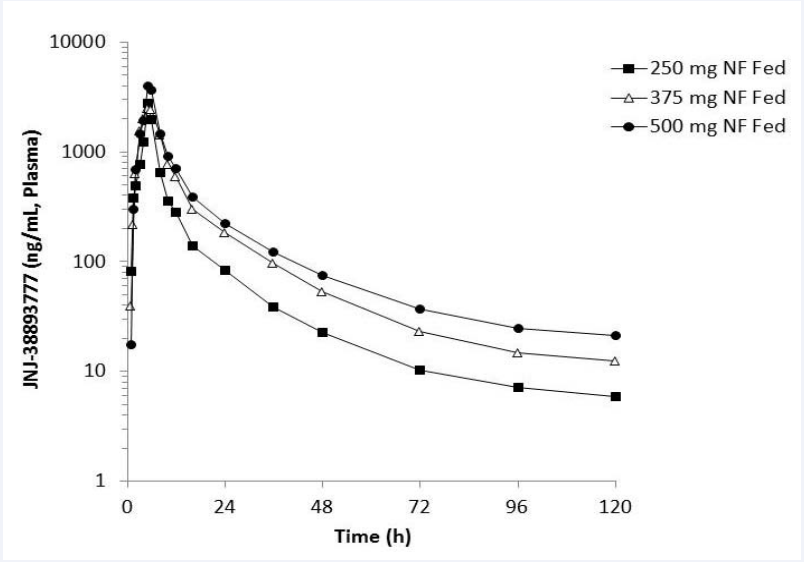

Figure 4 Mean (SD) Plasma Concentrations-Time Profiles Of JNJ-38893777 Following Single Oral Administration of a New Tablet Formulation (NF) to Healthy Men under Fed Conditions in Part 2.

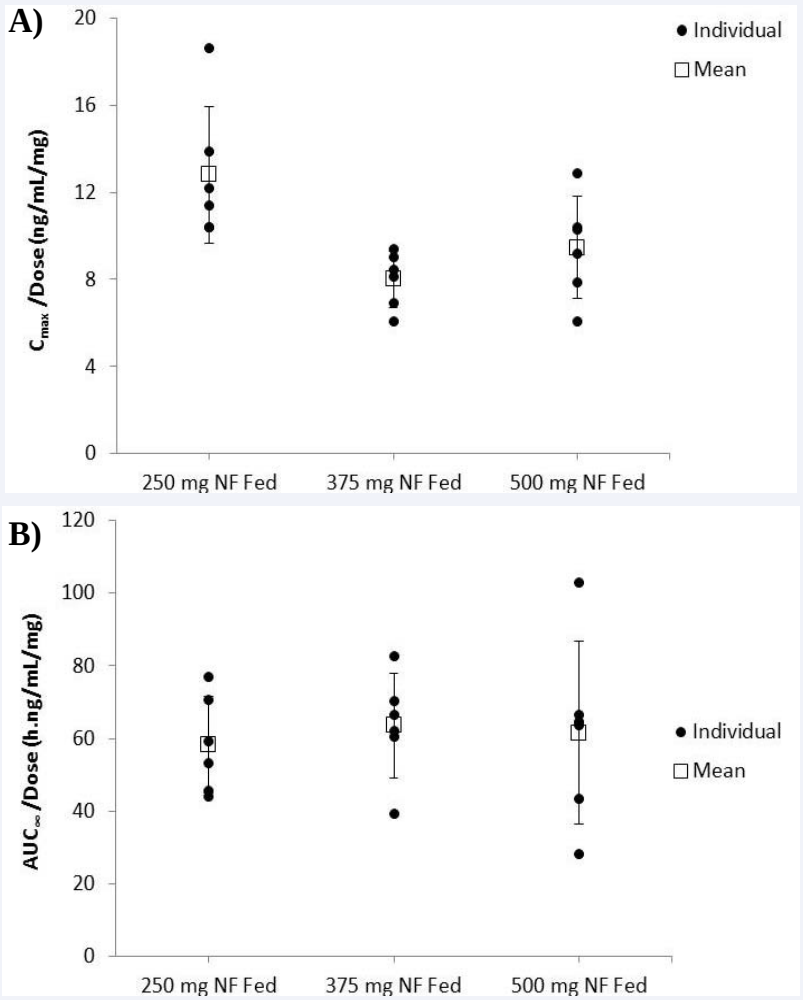

Figure 5 Relationship Between Dose Normalized C_{max} and Dose Normalized AUC_{∞} Versus Different JNJ-38893777 Doses Following Single Oral Administration of a New Tablet Formulation Under Fed Condition in Part 2.

reported during the study were mild to moderate in severity.

There were no changes in the vital signs, electrocardiograms and laboratory parameters in any of the treatment groups.

DISCUSSION

JNJ-38893777 is a potent TRPV1 receptor antagonist being considered for the development for the treatment of pain. In this first-in human study, JNJ-38893777 was administered to healthy participants using two different tablet formulations as single ascending oral doses ranging from 5 to 500 mg for the original formulation under fasting condition, and 250 to 500 mg as a new formulation under fed condition. Additionally, the effect of a high fat meal on the bioavailability of JNJ-38893777 from the new formulation was evaluated at the 250 mg dose. The safety, tolerability, pharmacokinetics, and pharmacokinetic/pharmacodynamic relationship (core body temperature and QTcF) were evaluated.

In Part 1 of the study, an original tablet formulation was used which resulted in a less than dose proportional increase in exposure (C_{max} and AUC) for JNJ-38893777 with high variability as much as 166%. The observed increases in CL/F and Vd_z/F with increasing doses may be due to a decrease in oral bioavailability (F) of JNJ-38893777 as doses increased. Since JNJ-38893777 is a BCS (Biopharmaceutical Classification System) class 2 compound with high membrane permeability and poor water solubility [18], it is possible that the in vivo dissolution of the tablet in the gastrointestinal tract may have decreased as doses increased, leading to decreasing oral bioavailability.

Due to poor bioavailability of JNJ-38893777 from the original tablet formulation, a new tablet formulation with hydroxypropyl methylcellulose was developed and used in Part 2 to determine whether bioavailability of JNJ-3889377 can be improved and the MTD can be attained. The results showed that adding hydroxypropyl methylcellulose to the new tablet formulation did not improve bioavailability of JNJ-38893777 under fasting conditions. Mean C_{max} and AUC_{∞} values decreased by 60% and 18%, respectively, with the new tablet formulation relative to the original formulation. However, the variability in C_{max} and AUC values for the new tablet formulation (85% and 73%, respectively) was improved compared with those for the original formulation (166% and 99%, respectively). These results are consistent with the findings for any BCS class 2 compounds. It is possible that

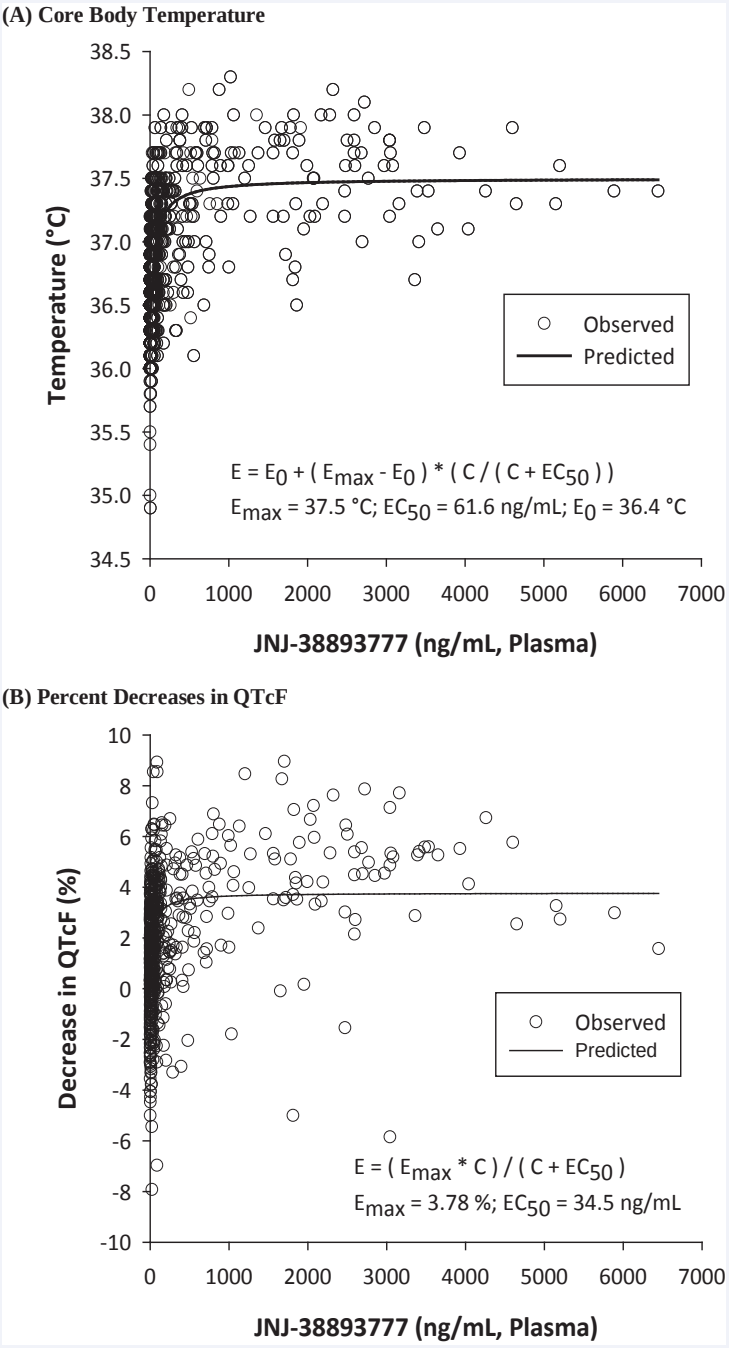

Figure 6 Relationship Between Core Body Temperature (A) and Percent Decreases in QTcF (B) Versus Plasma Concentrations of JNJ-38893777 Following Single Oral Administration Of JNJ-38893777 as Tablet Formulation, Data Pooled From Both Part 1 and Part 2.

hydroxypropyl methylcellulose, a binding agent, may retard the dissolution of JNJ-38893777 in the gastrointestinal tract under fasting condition.

Based on the physicochemical characteristics of the compound as a BCS class 2, it was postulated that dosing with a high-fat meal may increase in vivo dissolution and hence increase the bioavailability of JNJ-38893777. The food effect aspect was initially evaluated at a 250 mg dose of the new formulation, and the result was as expected. Thus, dose escalation to attempt to reach the MTD was continued in the fed state. A high-fat meal increased the bioavailability of JNJ-38893777 from the new tablet formulation by 11- to 22-fold and inter-individual variability of C_{max} and AUC_{∞} was reduced from 85% and 73%, respectively to 24% and 23%, respectively. Additionally, mean $t_{1/2}$ was extended from 23.3 hour to 51.2 hour, which may result from a continuous absorption from the lower gastrointestinal tract. It must be noted that because of the high-fat meal, safety and tolerability evaluation at high exposures was possible.

The starting dose in this study was successfully selected. The mean C_{max} value (20 ng/mL) of the starting dose of 5 mg

Table 3: Most Commonly Reported (in >10% Participants) Treatment- Emergent Adverse Events in All Groups.

	Placebo N=20 n (%)	5 mg (fasted) N=6 n (%)	15 mg (fasted) N=6 n (%)	45 mg (fasted) N=6 n (%)	125 mg (fasted) N=6 n (%)	250 mg (fasted) N=6 n (%)	500 mg (fasted) N=6 n (%)	250 mg NF (fasted) N=6 n (%)	250 mg NF (fed) N=6 n (%)	375 mg NF (fed) N=6 n (%)	500 mg NF(fed) N=6 n (%)	Total Active treatment N=60 n (%)
Total no of participants with TEAEs	9 (45)	2 (33)	3 (50)	4 (67)	5 (83)	3 (50)	4 (67)	4 (67)	6 (100)	6 (100)	5 (83)	42 (70)
Pyrexia	0	0	0	0	0	0	2 (33)	0	6 (100)	3 (50)	4 (67)	15 (25)
Feeling cold	0	0	0	0	0	0	1 (17)	0	2 (33)	3 (50)	1 (17)	7 (12)
Hypoesthesia	0	0	0	0	0	0	0	0	3 (50)	1 (17)	2 (33)	6 (10)
Paresthesia	1 (5)	0	0	1 (17)	0	0	0	0	1 (17)	2 (33)	2 (33)	6 (10)
Feeling hot	0	0	0	0	2 (33)	0	0	0	2 (33)	0	1 (17)	5 (8)
Headache	4 (20)	0	3 (50)	0	0	0	0	0	2 (33)	0	0	5 (8)
Dizziness	2 (10)	1 (17)	0	0	0	0	1 (17)	0	2 (33)	0	0	4 (7)

NF: New Formulation; TEAE: Treatment-Emergent Adverse Event

was within the predicted concentration (17-66 ng/mL) which was lower than the minimal effective concentrations observed in relevant preclinical in vivo assays (177 - 1073 ng/mL, unpublished observation). The results also confirmed that the allometric scaling [17] method was successfully used to predict clearance, volume of distribution, and exposure in humans based on preclinical data.

There was a statistically significant increase in heat pain detection threshold and the heat pain tolerance limit in participants receiving JNJ-38893777 in the fed state compared with those receiving placebo. These results are in agreement with heat pain detection threshold of the non-sensitized skin of participants following another TRPV1 antagonist [19]. The timing of the heat pain detection threshold and heat pain tolerance assessments were based on the t_{max} observed for JNJ-38893777.

Overall, the compound was well-tolerated at single oral doses up to 500 mg. The highest exposure achieved (AUC_{∞}=30,735 ng.h/mL) was similar to the NOAEL (28,300 ng.h/mL in male rat), and no safety findings related to the toxicity were observed.

As expected based on the mechanism of action of the compound, mild dose-dependent increases in body temperature were observed in some participants. The maximum body temperature observed was 38.5ºC and all increases in temperature were well tolerated and resolved without intervention. This is consistent with preclinical pharmacology studies in conscious dogs in which JNJ-38893777 was associated with an increase in core body temperature of 1 to 2ºC. It is also consistent with the effects of other TRPV1antagonists on body temperature reported in the literature [20], which demonstrated a plasma-concentration dependent 1 to 2ºC increase in body temperature following administration of a TRPV1 antagonist in healthy volunteers. Although the mechanism underlying the JNJ-38893777 induced increase in body temperature is not clear, TRPV1 being a thermo sensor expressed in thermo sensing sensory afferents and in the hypothalamus [5], it is postulated that blockade of TRPV1 activates a physiological "cold defense" response involving sympathetic activation and peripheral vasoconstriction and/or thermogenesis [21]. Preclinical studies have demonstrated that JNJ-38893777 does not increase oxygen consumption in rats, thus suggesting that the increased body temperature may not be due to thermogenesis.

The actions of TRPV1 antagonists other than JNJ-38893777 have been characterized across species [19,20]. Similar to these TRPV1 antagonists, JNJ-38893777 is a small molecule that is a competitive antagonist of the TRPV1 receptor lacking agonist activity and thus would not be expected to dangerously exaggerate the pharmacologic activity. The compound has excellent pharmacokinetic properties (moderate to high absorption, low clearance) across species and demonstrates acceptable safety margins in both rat and dog 4-week toxicology studies. The pharmacological effects are found to be dose- and concentration-dependent, and hence predictable. Taking this into account, JNJ-38893777 would not be considered a high-risk compound necessitating dosing below the MABEL in humans. However, to provide an additional level of protection, a starting dose of 5 mg (6-fold lower than the MRSD of 34 mg) was chosen.

CONCLUSION

This was the first planned clinical study that evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of single ascending oral doses of JNJ-38893777 in healthy men. Subsequent studies are necessary to evaluate multiple ascending oral doses of JNJ-38893777 in healthy men, and the efficacy of JNJ-38893777 in studies of potential pain and non-pain indications.

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Conflict of Interest

All authors are employees of Janssen Research & Development. All authors meet ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors hold stock in the company. All authors had access to the study data and made the final decision about where to publish these data.

Registration

EudraCT Number: 2008-000206-37

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