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An oral TRPV1 antagonist attenuates laser radiant-heat-evoked potentials and pain ratings from UV_B-inflamed and normal skin

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- ABT-102, a novel TRPV1 antagonist, has demonstrated efficacy in several preclinical models of pain. Laser (radiant-heat) evoked potential amplitudes and pain visual analogue scales, approved in numerous past algesimetric studies, were used to evaluate the antinociceptive and antihyperalgesic effects of ABT-102 compared with placebo and two active controls in normal and UV_B-inflamed skin.

WHAT THIS STUDY ADDS

- The results obtained using this model indicated that ABT-102 was well tolerated and dose-dependently efficacious in reducing both thermal hyperalgesia and non-hyperalgesic pain. The algesimetric model showed reproducibility and confirmed its suitability in a small number of normal healthy subjects.

AIMS

Laser (radiant-heat) evoked potentials (LEPs) from vertex-EEG peak-to-peak (PtP) amplitude were used to determine acute antinociceptive/antihyperalgesic efficacy of ABT-102, a novel TRPV1 antagonist efficacious in preclinical pain models, compared with active controls and placebo in normal and UV_B-inflamed skin.

METHODS

This was a randomized, placebo- and active-controlled, double-blind, intra-individual, crossover trial. Twenty-four healthy subjects received six sequences of single doses of ABT-102 (0.5, 2, 6 mg), etoricoxib 90 mg, tramadol 100 mg and placebo. Painful stimuli were induced by CO_2-laser on normal and UV_B-inflamed skin. LEPs and visual analogue scale (VAS-pain) ratings were taken at baseline and hourly up to 8 h post-dose from both skin types.

RESULTS

Compared with placebo, significant mean decreases in the primary variable of LEP PtP-amplitude from UV_B-inflamed skin were observed with ABT-102 6 mg ($P < 0.001$), ABT-102 2 mg ($P = 0.002$), tramadol 100 mg ($P < 0.001$), and etoricoxib 90 mg ($P = 0.001$) over the 8 h period; ABT-102 0.5 mg was similar to placebo. ABT-102 6 mg was superior to active controls over the 8 h period ($P < 0.05$) whereas ABT-102 2 mg was comparable. Improvements in VAS scores compared with placebo were observed with ABT-102 6 mg ($P < 0.001$) and ABT-102 2 mg ($P = 0.002$). ABT-102 average plasma concentrations were 1.3, 4.4 and 9.4 ng ml^{-1} for the 0.5, 2 and 6 mg doses, respectively. There were no clinically significant safety findings.

CONCLUSIONS

TRPV-1 antagonism appears promising in the management of clinical pain, but requires further investigation.

Introduction

One of the greatest unmet needs in pain management exists in the treatment of moderate to severe chronic nociceptive pain [1]. Non-steroidal anti-inflammatory drugs (NSAIDs) have only modest effects on moderate to moderately severe pain and the treatment success of these agents is often limited by gastrointestinal and/or cardiovascular effects [2, 3]. The use of opioids, while effective in the management of moderate to severe pain, is complicated by gastrointestinal tolerability and sedation [4], as well as by concerns regarding tolerance and abuse potential [5–8]. New, effective, oral analgesics with acceptable safety profiles are truly needed.

Transient receptor potential vanilloid type 1 (TRPV1) receptors are activated in association with inflammation and other conditions in both acute and chronic nociceptive pain [9]. In addition to being found in all sensory ganglia, TRPV1 is expressed in the central nervous system, including certain regions of the brain. TRPV1 agonists include capsaicin and its functional analogues, low extracellular pH and heat > 43°C (for review see [10]). ABT-102 is a TRPV1 receptor antagonist, representing a novel mechanism of action for the treatment of nociceptive pain [11, 12]. ABT-102 has demonstrated efficacy in pre-clinical models of acute and chronic nociceptive pain of both cancer and non-cancer aetiology [13].

Measurements of pain in clinical studies typically employ self-reported rating scales such as the visual analogue scale (VAS). However, more quantitative electrophysiological measures of brain activity in cortical regions that process painful stimuli and integrate and interpret pain have been established [14–16]. Laser (radiant-heat) evoked potentials (LEPs) are a neurophysiological way to measure the central nervous system projection of pain pathways and the integration into pain perception after CO_2 laser-induced activation of thinly myelinated cutaneous nociceptors. After repeated stimuli to the skin, evoked potentials can be recorded from the vertex position by electroencephalographic (EEG) surface electrodes after filtering and averaging. The amplitude of the peak-to-peak (PtP) waveform increases with the perceived intensity of experimentally induced acute pain, and known analgesics have been shown to reduce the PtP-amplitude (for review see [17]).

Here we report the results of a study conducted in healthy human subjects investigating the antinociceptive and antihyperalgesic effects of different ABT-102 doses, a partial opioid receptor agonist (tramadol), a COX-2 inhibitor (etoricoxib) and placebo in a model of experimentally induced pain. Mild to moderate pain was induced by repeated CO_2 laser stimulation to ultraviolet (UV_B)-irradiated/-inflamed skin and to normal skin. A correlate of perceived pain was measured by LEP amplitudes detected by vertex-EEG, and retrospective VAS pain scores were registered after each LEP session. ABT-102 pharmacokinetics (PK) were also characterized during the course of the trial.

Methods

Study design

This was a phase 1, single dose, randomized, double-blind, placebo- and active-controlled, six period, intra-individual complete crossover study carried out at a single centre in Germany. The study was conducted in accordance with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP). Ethics committee approval (Bavarian Chamber of Physicians, Munich, Germany) and signed informed consent forms were obtained prior to any study procedures. Receptor nomenclature in this report conforms to the 5th edition of the British Journal of Pharmacology Guide to Receptors and Channels [18].

The primary study objective was to compare the efficacy of single doses of ABT-102 (0.5, 2 and 6 mg), tramadol and etoricoxib with placebo in healthy subjects with mild to moderate pain stimuli. The ABT-102 doses in this study were selected to provide exposure levels comparable with those evaluated in other clinical trials [19, 20]. These levels were predicted to be efficacious based on experiments in preclinical models of pain [13].

A schematic of the study design and treatment sequences is presented in Figure 1. The duration of the study was approximately 9 weeks. A screening visit 2 to 14 days prior to the first dose of study drug was conducted to determine subject eligibility. Eligible subjects then returned for a total of six assessment periods. Subjects were randomized in an equal number to one of six treatment sequences of single doses of ABT-102 (0.5, 2 and 6 mg), tramadol 100 mg, etoricoxib 90 mg and placebo, applying a Williams design [21]. The randomization schedule was produced by the Department of Statistics at Abbott. Safety follow-up was conducted at the end of the last assessment period.

The crossover study, planned with a total of 24 subjects, was to detect a treatment difference at a two-sided 5% significance level with a statistical power of 80%, if the true difference of the target variable between the treatment groups was 1.6 amplitude units (μV). This was based on the assumption that the within-subject standard deviation of the response variable was 5.6 μV. The crossover design of this study comparing multiple regimens provides within-subject comparisons thus increasing the statistical power. Additionally, the randomized treatment sequences provide well-controlled comparisons of the regimens. The 7 day washout period between doses was considered sufficient to prevent drug carryover.

Subjects

Healthy males 18 to 60 years of age with a body mass index (BMI) $\geq$18.0 kg m^{-2} and $\leq$29.0 k m^{-2} were eligible to participate in the study. Subjects were excluded if they had widespread acne, tattoos, scars or any pathogenic dermatological conditions at the sites for UV and laser exposures

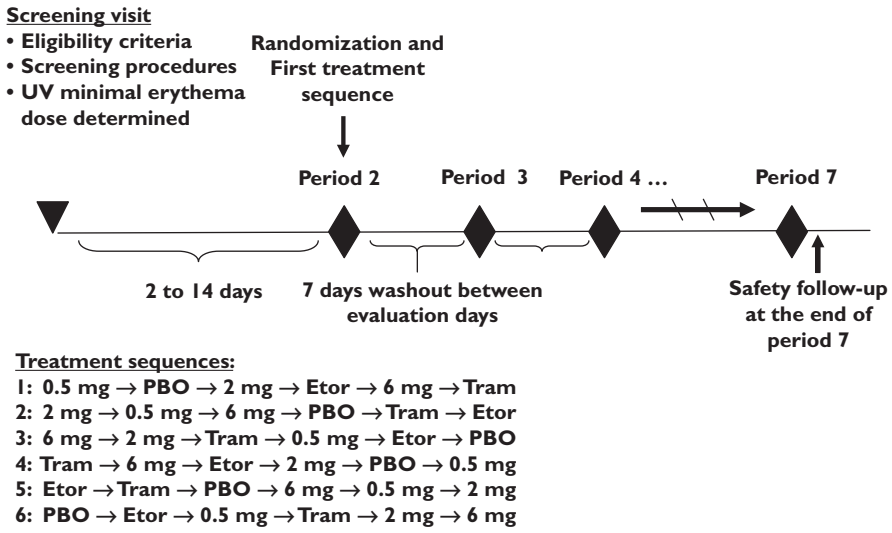

Figure 1

Study design. 0.5 mg, 2 mg and 6 mg = dose of ABT-102; Etor = etoricoxib; PBO = placebo; Tram = tramadol

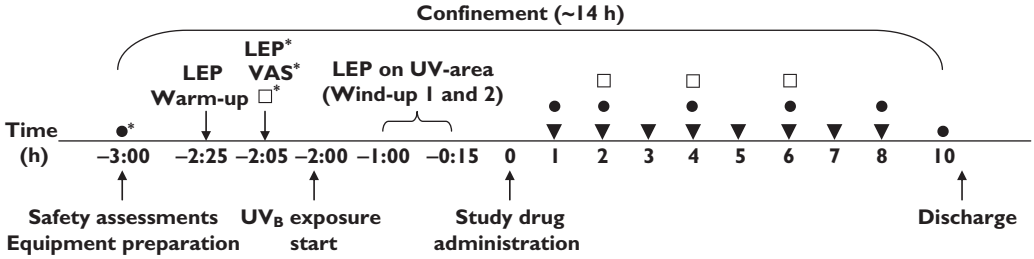

Figure 2

Procedure timing relative to study drug administration. LEP = laser evoked potential; UV_B = ultraviolet burn; VAS = visual analogue scale. *, Baseline assessment; ▼, LEP and VAS on normal and UV_B-irritated skin; •, Pharmacokinetic sampling; □, Skin reflection spectrometry measurement

on the back. Subjects were also excluded if they had allergies to any of the reference drugs, components of the study drug or drug administration vehicle, required regular use of medications, had used investigational drugs or drugs that induce cytochrome P450 3A4-induced metabolism within 1 month of study start, or had any clinically significant findings or medical history that precluded the subject from participating. Subjects were prohibited from using topical drugs or cosmetics on the sites for laser and UV exposures and were to refrain from sunbathing from 2 weeks prior to the first dose until the end of the study.

Study procedures

The timing of procedures and assessments relative to study drug administration for each assessment period is illustrated in Figure 2. UV irradiation (UV_B 290 to 320 nm wave length) was applied at the screening visit in ascending doses (corresponding to different irradiation times) to six different small areas of skin on the back to determine the individual minimum dose of UV_B that produced the first clearly discernible erythema. The two-fold individual minimal erythema dose (MED) of UV_B was applied to skin on the back to produce a homogeneous area of skin erythema and hyperalgesia 2 h prior to study drug administration at each medication period. The UV_B-treated area was large enough (5 × 5 cm) to perform repeated laser stimulations at varying locations on each assessment day. Two 'wind-up' or kindling laser stimulation sessions on UV_B-treated skin were performed prior to study drug administration to enhance hyperalgesia development.

ABT-102 and matching placebo were provided as oral solutions. Commercial formulations of 50 mg tramadol capsules (Aliud Pharma) and 90 mg etoricoxib tablets (MSD, Merck, Sharp & Dohme) were utilized. Placebos for tramadol and etoricoxib were manufactured by the sponsor. A designated, unblinded member of the clinical site staff not involved with any other aspects of trial conduct prepared the study drug solution according to protocol-specified instructions.

Each dose of study drug was taken orally after a standard breakfast. As the tramadol and etoricoxib placebos were not precisely identical to their corresponding active drugs, subjects were blindfolded for dosing. To maintain further the blind, subjects were not allowed to handle placebo capsules or tablets, and swallowed them directly from a dispensing cup. ABT-102 and placebo were administered with approximately 100 ml of Ensure Plus® (Abbott Laboratories), a commercial nutritional supplement primarily consisting of water, corn maltodextrin, sugar, milk protein concentrate, canola oil, corn oil and soy protein isolate [22]. This was followed by another 100 ml of Ensure Plus in the same container to recover any residual study drug. Ensure Plus was selected to mask taste differences between placebo and ABT-102. This method of administration was utilized in prior clinical trials of ABT-102 [19, 23]. Tramadol capsules, etoricoxib tablets and corresponding placebos were taken with 100 ml of tap water.

Pain was induced by repeated CO_2 laser stimuli (Pulsed CO_2-Laser, SYNRAD infrared gas LASER model E48-/- 26W, SYNRAD Inc., North Bothell, WA, USA) to normal skin and to the UV_B-inflamed skin at specific times after study drug administration. The normal skin evaluation was always performed first in each daily session sequence. The areas of UV and normal skin were randomly switched between the left and right sides of the back in each medication period, with UV exposure always occurring contralateral to the normal skin condition. The six UV_B sites were separated by dermatomes. Subjects were asked to perform a pursuit tracking task on a computer screen to stabilize/standardize vigilance while distracting from the painful laser stimuli and avoiding expectancy. A binaurally presented 80 dBA 'white' noise provided additional vigilance stabilization and masked acoustical cues.

Nociceptive processing was measured via LEP from vertex-EEG as PtP-amplitude as well as the single N2 and P2 components of the online LEPs averaging 12 artifact-free, Gaussian-phase-free-filtered vertex-EEG sections sampled with a digitization rate of 512 Hz after randomly presented laser stimuli, stepping aside by 2 to 3 mm after each stimulus, with a random inter-stimulus interval between 4 and 8 s and a stimulus duration of 60ms each using a beam diameter of 1.5 mm. Individual laser pain thresholds were determined at screening. Stimulus intensity was adjusted to 50% above pain threshold and kept constant throughout the entire study periods for each subject. LEP measurements from normal skin and UV-erythema were taken at baseline and 1, 2, 3, 4, 5, 6, 7 and 8 h post-dose (Figure 2), equivalent in timing to 3, 4, 5, 6, 7, 8, 9, and 10 h post 'acute' UV_B-irradiation in the morning of the main assessment days. The acute UV-irradiation paradigm evokes pathophysiological conditions, which are similar to 'acute' clinical pain (e.g., post-operative, post-traumatic states) with ongoing development of hyperalgesia and inflammation. Additionally, a self-reported paper and pencil 100 mm VAS was completed by the subjects immediately after each LEP session to assess the subjective overall pain estimate. To evaluate the anti-inflammatory effect of ABT-102, tramadol and etoricoxib, UV erythema intensity was measured by skin reflection spectrometry (Spectro 100® device, Instrument Systems, Munich, Germany) using Lab-system for redness definition (*a*-value).

Physical examinations, vital signs, ECGs and clinical laboratory evaluations (including tests of liver function) were performed in each period. Body temperature (aural), respiration rate, sitting blood pressure, and pulse rate were measured at screening, prior to dosing, at 1, 2, 3, 4, 5, 6, 7, 8 and 10 h post-dose, and prior to discharge from the study centre. Adverse events were assessed as reported throughout the study.

Pharmacokinetics

Blood samples for PK characterization of ABT-102 plasma concentrations were collected prior to dosing and at 1, 2, 4, 6, 8 and 10 h after dosing. The blood samples were collected via an indwelling cannula in 4 ml evacuated potassium ethylenediaminetetraacetic acid (EDTA)–containing collection tubes. The samples were centrifuged within 30 min of collection using a refrigerated centrifuge to separate the plasma. The plasma samples were frozen within 1 h after collection and maintained at −20°C or colder. Plasma concentrations of ABT-102 were determined using a validated liquid chromatography method with tandem mass spectrometric detection at Abbott Laboratories (Abbott Park, IL, USA). A highly sensitive bioanalytical method was utilized in the present study. This method has been previously published and the reader is referred to this publication for details on bioanalysis [24]. The lower limit of quantitation (LLOQ) was established at 0.011 ng ml^{-1} using a 300 µl plasma sample. The in-study calibration contained nine standards ranging from 0.011 to 12.2 ng ml^{-1}. All calibration curves had correlation coefficient values greater than or equal to 0.996. Samples quantified above the highest standard were diluted with blank plasma and re-assayed. Samples quantified below the lowest standard were reported as zero. In-study quality control samples demonstrated that the inter-run variability (% CV) ranged from 1.7 to 7.9% and the mean bias ranged from −3.3 to 2.6%.

ABT-102 maximum observed plasma concentration (C_{max}) and time to C_{max} (t_{max}), area under the curve from time 0 to 10 h post-dose ($AUC_{0\text{-}10}$) and average plasma concentration (C_{ave}) during the 10 h of measurement were estimated using non-compartmental analysis. The non-compartmental analysis was conducted using WinNonlin Professional software (Version 5.2; Pharsight Corporation, Mountain View, CA, USA).

Statistical analysis

The primary efficacy variable was the averaged (artifact-free) LEP PtP-amplitude from vertex-EEG leads after

repeated CO_2-laser stimulation of UV_B-inflamed skin. The secondary variables were LEP PtP-amplitude after repeated CO_2-laser stimulation of normal skin, LEP N2 and P2 amplitudes after repeated CO_2 laser stimulation of normal and UV_B-inflamed skin, VAS pain scores on repeated CO_2-laser stimulation of both skin conditions and the *a*-value of UV-erythema (CIE Lab-system). For LEP, VAS and UV-erythema intensity variables, a linear mixed effects model was employed. The model had fixed effects for baseline value (pre-dose measurement on normal skin for each period), sequence, time post-dose, treatment, period, interaction of treatment and time post-dose and interaction of period and time post-dose.

For the variance/covariance structure, compound symmetry was assumed within a period. Variances were assumed to be the same in all periods, but correlation of measurements in different periods was allowed to be smaller than the correlation of measurements within a period. For LEP and VAS variables, within the framework of the model, the hypothesis of no interaction between tramadol and placebo with time of measurement was tested at a significance level of 0.05. If this hypothesis was not rejected, the hypothesis of no difference between tramadol and placebo main effects was tested at level 0.05. Assuming that the performance of tramadol was satisfactory, the hypothesis of no difference between the highest ABT-102 dose and placebo was tested in the same way as for the comparison of tramadol and placebo. As judged appropriate from the results of these tests, additional tests for other pair-wise comparisons of treatments were performed.

All subjects who took at least one dose of study drug were included in the safety analyses. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 10.1 [25] and were tabulated by System Organ Class and MedDRA preferred term with a breakdown by treatment. Laboratory test values, vital sign measurements and ECG interval values that were potentially clinically significant according to predefined criteria were identified and listed separately. A linear mixed effects model like that described for the LEP variables was used for vital signs. Within the framework of the model, tests were performed to explore the possibility of effects of ABT-102 dose levels.

Results

Subjects

The 24 randomized subjects were healthy Caucasian males, Fitzpatrick skin type II through IV. The mean [standard deviation (SD)] age was 38.1 (6.65) years, mean (SD) body weight was 83.7 (8.61) kg and mean (SD) BMI was 25.2 (2.2) kg m^{-2}. All subjects completed all periods of the study.

Efficacy

Table 1 contains results over time for PtP-amplitude and VAS pain scores by treatment group and the mean differences from placebo over the 8 h period with associated 95% CIs. PtP-amplitude and VAS pain scores are presented graphically in Figures 3 and 4, respectively. Results for N2 and P2 amplitude changes for each treatment compared with placebo are presented in Table 2.

The statistic for the test on sequence effect was not significant for any variable, with a *P* value of 0.60 for the primary variable, with the smallest *P* value being 0.171 for the VAS pain score in normal skin. The statistical model accounted for any period effects, including the interaction of period with time post-dose. However, the statistics for these effects were not significant at the 0.10 level for any variable except redness in UV_B-inflamed skin, for which the statistics for both the interaction of period and time post-dose and for the period main effect (pertaining to the average over the several times) were significant at $P < 0.001$.

Primary efficacy variable: LEP PtP-amplitude reductions in UV_B-inflamed skin Results for the averaged (artifact-free) LEP PtP-amplitude from vertex-EEG leads after repeated CO_2-laser stimulation of hyperalgesic UV_B-inflamed skin are presented in Figure 3B. PtP-amplitude increased over time with placebo due to both increasing inflammation and the kindling effect of repeated laser sessions. For the primary outcome measure, statistically significant effects compared with placebo were observed with ABT-102 6 mg ($P < 0.001$), ABT-102 2 mg ($P = 0.002$), tramadol 100 mg ($P < 0.001$) and etoricoxib 90 mg ($P = 0.001$) for the average reduction in PtP-amplitude over 8 h. The peak effect of ABT-102 6 mg occurred at 2 to 3 h, consistent with time of maximum plasma exposure (Table 3). ABT-102 6 mg was more effective than placebo in reducing PtP-amplitude at **all** post-administration time points from 1 to 8 h. ABT-102 6 mg was superior to both active comparators over the 8 h period ($P < 0.05$). ABT-102 2 mg was comparable in effect with both active controls, whereas ABT-102 0.5 mg was similar to placebo.

Secondary efficacy variable: LEP PtP-amplitude reductions in normal skin LEP PtP results over time on normal, non-hyperalgesic skin are presented in Figure 3A. In contrast to UV_B-inflamed skin, no relevant development of hyperalgesia was observed in PtP-amplitude in normal skin after repeated CO_2-laser stimulation. ABT-102 6 mg, ABT-102 2 mg and tramadol 100 mg demonstrated a statistically significant reduction in PtP-amplitude compared with placebo over 8 h (all $P < 0.001$). ABT-102 6 mg was significantly more effective compared with both tramadol 100 mg ($P < 0.05$) and etoricoxib 90 mg ($P < 0.001$) for the average PtP reduction over 8 h post-dose. Etoricoxib 90 mg and ABT-102 0.5 mg exhibited placebo-like effects. Etoricoxib was statistically superior to placebo only in

Table 1

PtP-amplitude and VAS pain scores over time by treatment group ($n = 24$)

Time post-dose (h)	Pre-dose (0)	1	2	3	4	5	6	7	8	Mean difference from placebo over the 8 h period (95% CI)
PtP-amplitude in normal skin, Mean ± SD (μV)										
ABT-102 0.5 mg	21.1 ± 11.8	21.1 ± 9.9	19.7 ± 7.9	19.3 ± 7.7	22.4 ± 10.1	23.3 ± 9.8	22.4 ± 9.4	24.4 ± 10.1	23.2 ± 8.8	–1.21 (–3.75, 1.32)
ABT-102 2 mg	23.3 ± 9.6	18.8 ± 11.8	17.0 ± 8.7	16.9 ± 7.1	17.0 ± 7.5	17.6 ± 7.5	18.2 ± 10.3	19.1 ± 8.7	20.1 ± 5.5	**–5.81**** (–8.35, –3.27)
ABT-102 6 mg	21.9 ± 11.6	19.5 ± 12.1	15.1 ± 8.9	13.9 ± 8.7	12.7 ± 7.4	14.0 ± 6.7	16.9 ± 10.2	18.9 ± 11.2	17.5 ± 9.9	**–7.40**** (–9.93, –4.86)
Tramadol 100 mg	24.4 ± 10.4	23.2 ± 9.2	20.6 ± 8.8	20.1 ± 10.2	18.4 ± 8.3	18.3 ± 8.5	17.4 ± 8.4	20.1 ± 6.4	19.7 ± 10.1	**–4.47**** (–7.02, –1.92)
Etoricoxib 90 mg	21.9 ± 11.0	24.4 ± 12.6	21.3 ± 11.8	21.8 ± 13.2	25.8 ± 14.2	23.3 ± 11.4	22.0 ± 9.7	24.9 ± 10.3	23.5 ± 12.1	–0.16 (–2.69, 2.37)
Placebo	21.8 ± 9.4	21.7 ± 8.8	22.5 ± 9.5	22.9 ± 9.7	23.2 ± 9.6	23.3 ± 9.2	22.6 ± 10.3	26.8 ± 11.6	24.6 ± 10.8	–
PtP-amplitude in UV_B-inflamed skin, Mean ± SD (μV)										
ABT-102 0.5 mg	–	26.4 ± 13.5	28.8 ± 10.7	28.3 ± 9.9	30.3 ± 11.8	32.1 ± 10.3	32.1 ± 13.9	31.3 ± 11.3	32.0 ± 15.0	–1.81 (–4.32, 0.71)
ABT-102 2 mg	–	22.9 ± 10.3	24.4 ± 10.9	24.7 ± 13.2	27.8 ± 10.6	30.9 ± 10.2	33.0 ± 11.0	32.9 ± 10.5	33.7 ± 12.8	**–3.92**+ (–6.44, –1.40)
ABT-102 6 mg	–	23.1 ± 13.0	17.5 ± 10.9	18.8 ± 11.3	21.8 ± 13.5	24.2 ± 12.6	26.1 ± 11.4	28.3 ± 12.2	27.6 ± 9.7	**–8.81**** (–11.33, –6.30)
Tramadol 100 mg	–	28.2 ± 10.2	25.7 ± 10.9	27.3 ± 9.0	28.4 ± 11.9	28.6 ± 12.4	29.0 ± 11.1	28.8 ± 9.7	30.7 ± 9.8	**–4.60**** (–7.14, –2.07)
Etoricoxib 90 mg	–	29.9 ± 9.4	25.2 ± 7.0	24.3 ± 10.1	27.8 ± 8.2	27.5 ± 9.5	27.5 ± 8.6	29.4 ± 6.8	32.9 ± 10.6	**–4.17**** (–6.68, –1.65)
Placebo	–	27.5 ± 9.4	29.7 ± 12.9	31.3 ± 13.4	34.7 ± 13.4	34.0 ± 12.5	34.2 ± 11.6	32.4 ± 12.4	33.8 ± 12.1	–
VAS pain scores in normal skin, Mean ± SD (mm)										
ABT-102 0.5 mg	17.9 ± 14.2	18.6 ± 14.9	20.5 ± 14.7	22.0 ± 14.0	26.3 ± 17.0	28.4 ± 16.8	30.7 ± 18.7	34.2 ± 21.0	39.5 ± 22.7	–2.30 (–6.15, 1.54)
ABT-102 2 mg	17.0 ± 9.3	15.7 ± 8.7	17.5 ± 9.8	17.5 ± 10.0	20.9 ± 11.9	23.0 ± 11.8	24.9 ± 14.0	27.9 ± 17.8	31.5 ± 19.9	**–6.79**** (–10.64, –2.93)
ABT-102 6 mg	17.1 ± 9.3	16.6 ± 9.7	15.1 ± 7.8	15.4 ± 8.6	15.9 ± 8.8	17.7 ± 9.2	20.0 ± 10.4	23.8 ± 12.0	29.5 ± 14.2	**–10.04**** (–13.90, –6.19)
Tramadol 100 mg	17.5 ± 9.7	18.2 ± 10.3	18.7 ± 10.4	19.1 ± 10.6	20.8 ± 11.5	21.8 ± 12.5	23.5 ± 13.3	26.4 ± 16.2	31.2 ± 17.6	**–7.08**** (–10.93, –3.23)
Etoricoxib 90 mg	16.6 ± 10.9	18.4 ± 11.6	20.0 ± 13.4	22.0 ± 13.6	26.5 ± 16.1	29.6 ± 18.8	31.0 ± 19.1	33.6 ± 19.4	40.8 ± 23.2	–1.21 (–5.07, 2.65)
Placebo	19.0 ± 12.4	19.9 ± 11.6	23.6 ± 12.3	26.3 ± 15.0	28.9 ± 15.3	32.4 ± 18.5	35.1 ± 20.3	37.2 ± 21.7	41.2 ± 21.5	–
VAS pain scores in UV_B-inflamed skin, Mean ± SD (mm)										
ABT-102 0.5 mg	–	31.4 ± 20.0	35.0 ± 20.6	39.3 ± 21.8	44.9 ± 24.7	49.5 ± 25.5	52.9 ± 25.2	56.8 ± 25.6	60.6 ± 26.3	–1.30 (–6.02, 3.42)
ABT-102 2 mg	–	24.1 ± 12.4	25.7 ± 13.3	30.9 ± 15.8	36.9 ± 20.3	43.0 ± 23.5	48.4 ± 27.0	52.9 ± 27.6	54.5 ± 29.9	**–7.38**+ (–12.11, –2.65)
ABT-102 6 mg	–	24.5 ± 9.9	21.9 ± 8.2	24.6 ± 8.1	27.4 ± 9.3	31.0 ± 11.4	38.7 ± 15.6	44.1 ± 17.0	50.7 ± 20.5	**–14.18**** (–18.91, –9.45)
Tramadol 100 mg	–	29.8 ± 13.5	31.3 ± 15.0	33.4 ± 15.0	37.1 ± 17.7	43.0 ± 21.3	45.0 ± 22.2	47.2 ± 22.0	52.1 ± 24.3	**–7.46**+ (–12.18, –2.73)
Etoricoxib 90 mg	–	29.8 ± 14.6	31.5 ± 15.0	33.3 ± 16.4	38.3 ± 18.4	43.6 ± 22.1	46.5 ± 24.7	49.8 ± 25.0	55.5 ± 26.7	**–5.65**+ (–10.39, –0.91)
Placebo	–	29.5 ± 13.1	35.4 ± 15.2	41.3 ± 17.9	46.9 ± 20.3	52.1 ± 23.1	57.0 ± 23.8	60.8 ± 23.4	64.3 ± 24.1	–

Pre-dose values collected for normal skin type only. Statistically significant values in bold type; $+P \leq 0.05$ *vs.* placebo; ** $P \leq 0.001$ *vs.* placebo. LEP, laser evoked potential; PtP, peak-to-peak amplitude; UV_B, ultraviolet burn; VAS, visual analogue scale.

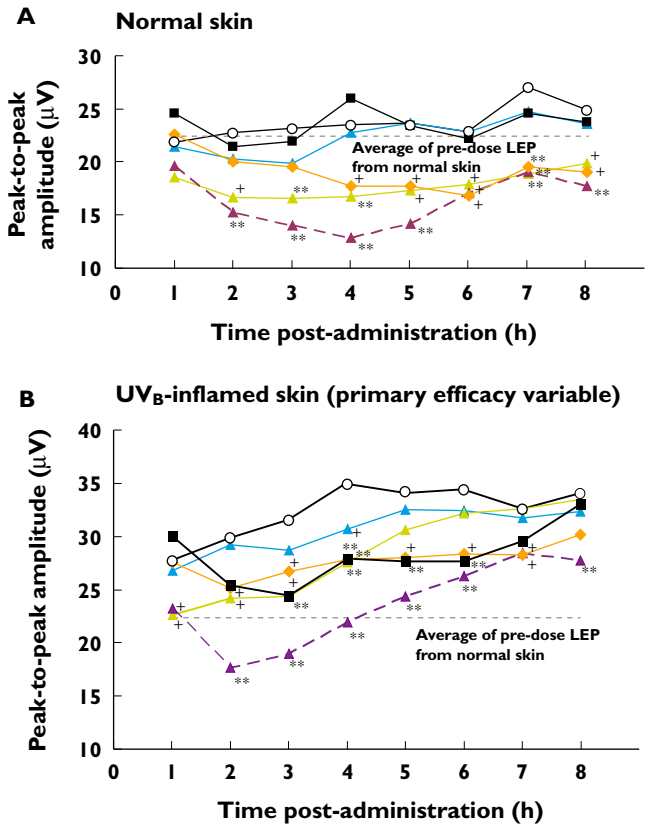

Figure 3

LEP PtP-amplitude over time in normal skin (A) and UV_B-irritated skin (B) for all randomized subjects ($n = 24$). +$P \leq 0.05$ compared with placebo; **$P \leq 0.001$ compared with placebo. –▲–, ABT-102 0.5 mg; –▲–, ABT-102 2 mg; –▲–, ABT-102 6 mg; –◆–, Tramadol 100 mg; –■–, Etoricoxib 90 mg; –○–, Placebo

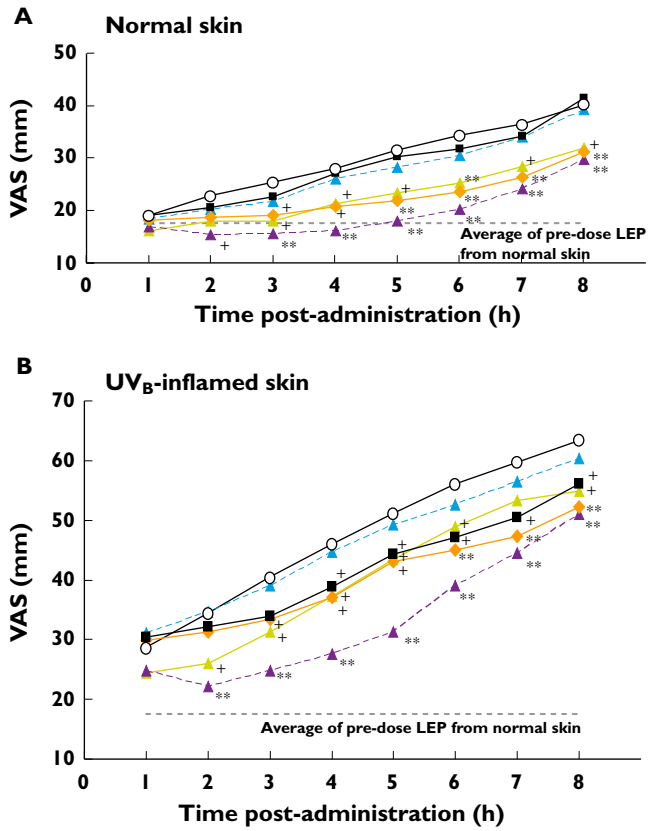

Figure 4

VAS pain scores over time in normal skin (A) and UV_B-irritated skin (B) for all randomized subjects ($n = 24$). +$P \leq 0.05$ compared with placebo; **$P \leq 0.001$ compared with placebo. (–▲–, ABT-102 0.5 mg; –▲–, ABT-102 2 mg; –▲–, ABT-102 6 mg; –◆–, Tramadol 100 mg; –■–, Etoricoxib 90 mg; –○–, Placebo

UV_B-inflamed skin. Placebo treatment values were relatively constant over time, thus demonstrating no circadian rhythm or habituation to repeated laser sessions over the daily time course.

Secondary efficacy variables: LEP single N2 and P2 component amplitudes in both skin types The results of the single LEP-components (N2, P2) for UV_B and normal skin supported the major findings for the overall PtP amplitudes in both skin types. As a sign of hyperalgesia they generally demonstrated higher amplitudes for the irritated UV_B-inflamed skin than seen in the normal skin condition. Both skin sites obviously showed a higher amplitude reduction in the earlier N2 *vs.* the later appearing P2 amplitude, especially for the highest ABT-102 dose (6 mg, Table 2).

Secondary efficacy variable: VAS pain scores in normal skin In contrast to UV-exposed skin, the VAS pain scores rose only slightly but continuously over 8 h in the normal skin upon repeated CO_2-laser stimulation (Figure 4A). In normal, non-hyperalgesic skin, ABT-102 6 mg, ABT-102 2 mg and tramadol 100 mg showed significant improvement compared with placebo for the average post-dose reduction over 8 h (all $P < 0.001$). ABT-102 6 mg was numerically better than tramadol 100 mg at all time points and was significantly better than etoricoxib 90 mg for the average post-dose reduction over 8 h ($P < 0.001$) in normal skin. The effect of ABT-102 2 mg was significant compared with etoricoxib in the average VAS pain scores over the 8 h period ($P = 0.004$) and comparable with tramadol 100 mg. The effect of ABT-102 0.5 mg was similar to the effects of placebo and etoricoxib.

Secondary efficacy measure: VAS pain scores in UV_B-inflamed skin The VAS pain scores increased much more steeply in UV_B-inflamed skin upon repeated CO_2-laser stimulation *vs.* non-UV-exposed (normal) skin (Figure 4B). ABT-102 6 mg prevented this increase for at least 3 h after intake. Over 8 h ABT-102 6 mg and 2 mg showed

Table 2

LEP N2 and P2 component amplitude changes compared with placebo in UV_B-inflamed and normal skin

	Time post-dose (h)								Average over the 8 h period (95% CI)
	1	2	3	4	5	6	7	8	
N2 amplitude: UV_B-inflamed skin (LS means, μV)									
ABT-102 0.5 mg	–0.81	–1.02	–1.26	–1.69	–2.05	–0.90	–1.27	–0.99	–1.25 (–2.72, 0.22)
ABT-102 2 mg	**–3.00**+	**–3.92****	**–4.18****	**–3.79****	–1.96	–1.23	0.70	–0.14	**–2.19**+ (–3.67, –0.71)
ABT-102 6 mg	**–2.69**+	**–6.91****	**–6.96****	**–6.52****	**–6.44****	**–5.40****	**–2.70**+	**–3.23**+	**–5.11**** (–5.11, –6.58)
Tramadol 100 mg	0.06	–1.70	–2.12	**–2.49**+	**–3.27**+	**–3.36**+	**–2.75**+	–1.85	**–2.19**+ (–3.66, –0.71)
Etoricoxib 90 mg	1.14	**–2.78**+	**–3.24**+	**–3.23**+	**–3.88****	**–2.68**+	–1.59	–0.42	**–2.08**+ (–3.55, –0.61)
N2 amplitude: normal skin (LS means, μV)									
ABT-102 0.5 mg	–0.15	–1.98	–2.26	–0.81	–0.58	–0.04	–0.75	–2.06	–1.08 (–2.49, 0.33)
ABT-102 2 mg	–1.66	**–3.20**+	**–3.50**+	**–4.26****	**–3.80****	**–2.62**+	**–4.58****	**–4.28****	**–3.49**** (–4.91, –2.07)
ABT-102 6 mg	–0.61	**–4.48****	**–4.60****	**–6.16****	**–5.59****	**–3.24**+	**–4.24****	**–5.16****	**–4.26**** (–5.67, 2.85)
Tramadol 100 mg	0.80	–1.04	–1.51	**–3.45**+	**–3.31**+	**3.18**+	**–3.19**+	**4.84****	**–2.46**** (–3.88, –1.05)
Etoricoxib 90 mg	1.05	–0.36	0.07	1.83	0.10	0.42	–0.67	–1.44	0.12 (–1.29, 1.53)
P2 amplitude: UV_B-inflamed skin (LS means, μV)									
ABT-102 0.5 mg	–0.08	0.40	–1.58	**–2.47**+	0.32	–1.00	0.40	–0.64	–0.58 (–1.88, 0.72)
ABT-102 2 mg	–2.00	–1.73	**–2.90**+	**–3.44**+	–1.58	–0.93	–0.59	–0.31	**–1.69**+ (–2.98, –0.39)
ABT-102 6 mg	–1.75	**–5.24****	**–5.63****	**–6.39****	**–3.45**+	**–2.74**+	–1.45	**–3.02**+	**–3.71**** (–5.01, –2.41)
Tramadol 100 mg	–0.01	**–2.93**+	**–2.57**+	**–4.41****	**–2.80**+	**–2.53**+	–1.50	–1.87	**–2.33**** (–3.63, –1.02)
Etoricoxib 90 mg	1.24	–1.69	**–3.80****	**–3.69****	**–2.69**+	**–4.06****	–1.45	–0.50	**–2.08**** (–3.38, –0.78)
P2 amplitude: normal skin (LS means, μV)									
ABT-102 0.5 mg	–0.34	–0.44	–0.97	0.11	0.77	–0.01	–1.49	0.80	–0.19 (–1.53, 1.14)
ABT-102 2 mg	–1.59	**–2.62**+	**–2.82**+	**–2.32***	**–2.18**+	–2.16	**–3.42**+	-0.54	**–2.21**** (-3.54, –0.87)
ABT-102 6 mg	–1.62	**–2.84**+	**–4.35****	**–4.33****	**–3.62****	**–2.47**+	**–3.65****	–1.91	**–3.10**** (–4.44, –1.76)
Tramadol 100 mg	–0.05	–1.48	–1.95	–2.15	**–2.36**+	**–2.72**+	**–4.14****	–0.82	**–1.96**** (–3.30, –0.61)
Etoricoxib 90 mg	1.59	–0.86	–1.22	0.73	–0.10	–1.06	–1.70	0.34	–0.29 (–1.62, 1.05)

Statistically significant values in bold type; +$P \leq 0.05$ *vs.* placebo; **$P \leq 0.001$ *vs.* placebo. LS, least-squares; LEP, laser evoked potential; UV_B, ultraviolet burn.

Table 3

ABT-102 pharmacokinetic parameters (mean ± SD) during the course of the experiment

Pharmacokinetic parameters (Units)	ABT-102 dose 0.5 mg	2 mg	6 mg
n	24	24	24
t_{max} (h)	2.2 ± 0.7	2.2 ± 0.6	2.8 ± 1.0
C_{max} (ng*hr ml^{-1})	2.1 ± 0.6	7.0 ± 1.7	14.9 ± 4.3
C_{ave} (ng*hr ml^{-1})	1.3 ± 0.3	4.4 ± 1.0	9.4 ± 2.5
$AUC_{0\text{-}10}$ (ng*hr ml^{-1})	13.0 ± 3.4	44.1 ± 10.3	93.9 ± 25.1

$AUC_{0\text{-}10}$, area under the plasma concentration–time curve from time 0 to 10 h post-dose; C_{ave}, average plasma concentration; C_{max}, maximum observed plasma concentration; t_{max}, time to maximum observed plasma concentration.

significant improvements in VAS pain scores compared with placebo for the average post-dose reduction over 8 h ($P < 0.001$ and $P = 0.002$, respectively). ABT-102 6 mg demonstrated a significant decrease in VAS pain score compared with tramadol 100 mg ($P = 0.005$) and etoricoxib 90 mg ($P < 0.001$) for the average post-dose reduction over 8 h. Both tramadol 100 mg ($P = 0.002$) and etoricoxib 90 mg ($P = 0.019$) were superior to placebo for the average post-dose reduction over 8 h. ABT-102 2 mg was comparable with the active controls, while ABT-102 0.5 mg was similar to placebo.

Evaluation of skin redness in UV_B-inflamed skin With respect to skin redness measured by reflection spectrometry (*a*-value of Lab-system), all doses of ABT-102 and tramadol 100 mg demonstrated negligible differences compared with placebo. Etoricoxib 90 mg had a significant attenuating effect compared with placebo on skin redness for the average post-dose reduction over 6 h ($P = 0.001$).

Pharmacokinetics

The PK parameters characterizing ABT-102 exposure during the course of the experiment are reported in Table 3. The time of ABT-102 maximum plasma exposure (t_{max}) was 2 to 3 h on average in the current study. As the dose increased from 0.5 to 6 mg, ABT-102 maximum concentration increased from 2.1 to 14.9 ng ml^{-1} and the average concentration increased from 1.3 to 9.4 ng ml^{-1}. The variability in ABT-102 exposure was modest (%CV less than 30% for C_{max} and AUC).

Safety

There were no serious adverse events and all treatment-emergent adverse events were mild in severity. Twenty of 24 (83%) participants reported at least one treatment-emergent adverse event. The most frequently reported adverse event in subjects taking ABT-102 was feeling cold, reported by 10 subjects (42%) in the 6 mg group and six subjects (25%) in the 2 mg group. There was a transient

dose-dependent effect on temperature compared with placebo (range 0.1 to 0.9°C). In the ABT-102 dose groups, body temperature ranged from 35.9°C (ABT-102 2 mg) to 38.1°C (ABT-102 6 mg), compared with a range of 35.6°C to 37.7°C in subjects taking placebo. No clinically significant changes were observed in liver function tests, or any other laboratory, vital sign or ECG parameter. No subject left the study prematurely due to an adverse event.

Discussion

This study investigated the efficacy of ABT-102 *vs.* placebo and the active comparators tramadol and etoricoxib in an experimental model of *acute* pain. ABT-102 was effective at two dose levels (2 mg and 6 mg) in reducing evoked pain in normal human subjects as assessed by the primary efficacy variable of LEP PtP-amplitude reduction in CO_2-laser (radiant-heat) stimulated UV_B-inflamed skin. These two dose levels of ABT-102 were also effective in normal non-inflamed skin although to a lesser extent, as expected from the particular role of TRPV1 in inflammatory thermal hyperalgesia [26, 27]. The effects of ABT-102 were clearly dose-dependent in both skin types. Comparable effects were observed in secondary LEP endpoints (single N2 and P2 component amplitudes). A smaller increase over hours in VAS pain scores was demonstrated with repeated CO_2-laser stimulation in normal skin, while the effect over time was consequently more pronounced in UV_B-inflamed skin with ongoing hyperalgesia development. Clear dose–responses in VAS pain score reduction in UV_B-inflamed and normal skin were also observed with ABT-102 treatment. Of note, ABT-102 6 mg was superior to tramadol 100 mg and etoricoxib 90 mg in UV_B-inflamed skin as measured by both LEP and VAS score. Etoricoxib was the only agent that demonstrated a statistically significant effect on erythema intensity compared with placebo, due to its anti-inflammatory properties that ABT-102 and tramadol do not possess.

Drug effects in reducing processing of both nociceptive/algesic and hyperalgesic stimuli were consistent when measured by LEP and VAS pain score. Additionally, the time course of observed drug effects was consistent with the plasma exposure t_{max} for ABT-102 (~2 to 3 h post-dose, Table 3), tramadol (~2 h post-dose) [28] and etoricoxib (~1 h post-dose) [29]. With active treatment, an earlier and greater magnitude of reduction was observed with the electrophysiological measure than with the subjective VAS pain assessment. This was indicated by smaller *P* values observed in the target variable when comparing PtP amplitudes *vs.* VAS pain with regard to placebo on the basis of the average of all eight LEP post-administration session time points in UV_B-inflamed skin for all five active treatments. The effect size estimate was correspondingly larger in the PtP amplitudes for all five active treatments.

The rank order of efficacy of the drugs was identical in the PtP amplitude and VAS outcome measures. The only discrepancy between LEP amplitudes and VAS scores over time was that the latter rose continuously in normal skin (under placebo, etoricoxib, and ABT-102 0.5 mg) while the former remained relatively constant, close to the pre-dose level. However, the effective analgesic drugs and doses (tramadol, ABT-102 2 mg and 6 mg) reduced or prevented this apparent increase in laser-induced pain ratings on normal skin. The design of the present study only allows speculation regarding the underlying cause of the discrepancy between LEP and VAS in non-hyperalgesic skin. The LEP is a measurable byproduct of cortical pain processing. Its amplitude correlates best with the subjective VAS score, which correlates well with the physical stimulus intensity [30, 31]. Cumbrousness and aversiveness (i.e. the affective attitude towards the painful stimuli) are not known to affect LEP amplitude, while it is conceivable that the VAS ratings are influenced by negative emotions accumulating during a long, boring day in the laboratory.

The use of etoricoxib and tramadol in the UV_B-inflamed skin and normal skin conditions served to validate the algesimetric model. The rationale for the introduction of the acute UV-irradiation paradigm (2 h pre-dosing) with developing erythema and hyperalgesia *vs.* a steady-state one is explained in the Methods section. In CO_2-laser stimulated UV_B-inflamed skin there is thermal hyperalgesia and up-regulation of TRPV1 receptor functions [32–34]. Under these conditions, etoricoxib 90 mg was effective in reducing PtP-amplitude, consistent with published anti-hyperalgesic effects [17, 35]. In CO_2-laser stimulated normal skin, where no inflammation would be expected, etoricoxib 90 mg was ineffective and placebo-like data were achieved. Tramadol was effective in both skin conditions, consistent with its opioid-like general analgesic mechanism of action. One can therefore conclude that the reductions in PtP-amplitude and VAS pain score observed in this experimental pain model are drug-specific and related to their mechanism of action.

ABT-102 exposure from the solution formulation increased dose-proportionally when administered under fed conditions [19]. In the present study, ABT-102 plasma exposure increased with dose in the 0.5 to 6 mg single dose range and the increase in exposure appeared to be less than dose-proportional (12-fold increase in dose resulted in 7-fold increase in exposure; Table 3). ABT-102 is a low solubility high permeability drug, the bioavailability of which increases with food with some formulations [23]. Therefore, administration of ABT-102 solution formulation following a 10 h fast in the present study is most likely responsible for the less than dose-proportional increase in exposure. Detailed reports of exposure–response analyses of the efficacy endpoints from the present study are warranted.

As typically seen with this class of compound, there was a dose-dependent increase in body temperature, with no increases above 39°C. The safety profile of ABT-102 differs

from that of MK-2295, another TRPV1 antagonist. Administration of MK-2295 showed an increase in heat pain threshold that remained after participants stopped taking the drug [36]. In the current study, heat pain threshold changes were observed with exposure levels but were transient and not associated with a permanent effect, consistent with trials investigating ABT-102 effects on thermosensory function [20]. The overall evidence suggests that the safety profiles of agents in this class vary depending on the individual compound under investigation.

ABT-102 was safe and generally well tolerated by subjects in this study. Confirmation of the detected ABT-102 antinociceptive and antihyperalgesic effect magnitude and its link to clinical relevance in analgesia can be drawn secondarily from a former meta-analytical approach, summarizing past studies with known clinically effective standard analgesics (e.g. from NSAID and opiate types) [17, 35]. In particular, the strong thermal antihyperalgesic effects may be beneficial in certain clinical pain conditions, because it has been demonstrated that the heat thresholds of TRPV1 (in cultured sensory neurons) as well as of cutaneous nociceptors can drop and remain below body temperature, if inflammation is mimicked by bradykinin application [37–39]. This is likely one reason why wounds, fractures, sprain and strain traumata and other sub-acute inflammatory conditions cause ongoing pain and why patients obtain benefit from cooling. In this way, the TRPV1 antagonist may mimic the analgesic effect of an ice pack without the risk of inducing cold pain.

The attrition of compounds in phase 2/3 of pharmaceutical development has an intense negative effect on pharmaceutical R&D productivity [40]. Attempts to minimize attrition are therefore imperative when planning how best to utilize available resources in pharmaceutical development. Applying methods to evaluate reliably the potential of drug candidates early in development is one way to enhance R&D output. As exemplified in this study, the LEP methodology is reproducible and can be used in a relatively small number of healthy subjects.

In conclusion, the collective results obtained using this model support the efficacy of ABT-102 for treatment of hyperalgesia and nociceptive pain. Further investigation is warranted to characterize the treatment effects of ABT-102 in the management of acute and chronic *clinical* pain.

Competing Interests

This study was funded by Abbott. W. Rachel Duan, Andrea E. Best, Ahmed A. Othman, Connie R. Faltynek, Charles Locke and Wolfram Nothaft are employees of Abbott. Klaus Schaffler was the principal investigator for the study. Klaus Schaffler and Peter Reeh have no reported conflicts of interest. The authors were assisted in the preparation of this manuscript by Muriel Cunningham, a professional medical writer compensated by Abbott.

REFERENCES

1 Katz WA, Barkin RL. Dilemmas in chronic/persistent pain management. Am J Ther 2008; 15: 256–64.

2 Koes BW, Scholten RJ, Mens JM, Bouter LM. Efficacy of non-steroidal anti-inflammatory drugs for low back pain: a systematic review of randomised clinical trials. Ann Rheum Dis 1997; 56: 214–23.

3 Langman MJ, Jensen DM, Watson DJ, Harper SE, Zhao PL, Quan H, Bolognese JA, Simon TJ. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 1999; 282: 1929–33.

4 Swegle JM, Logemann C. Management of common opioid-induced adverse effects. Am Fam Physician 2006; 74: 1347–54.

5 Morley-Forster PK, Clark AJ, Speechley M, Moulin DE. Attitudes toward opioid use for chronic pain: a Canadian physician survey. Pain Res Manag 2003; 8: 189–94.

6 National Institute on Drug Abuse. Research Report Series. Prescription drugs: abuse and addiction [online]. Updated 2005. Available at http://www.nida.nih.gov/researchreports/prescription/prescription.html (last accessed 15 July 2010).

7 Wolfert MZ, Gilson AM, Dahl JL, Cleary JF. Opioid analgesics for pain control: Wisconsin physicians' knowledge, beliefs, attitudes, and prescribing practices. Pain Med 2010; 11: 425–34.

8 Paulozzi LJ, Budnitz DS, Xi Y. Increasing deaths from opioid analgesics in the United States. Pharmacoepidemiol Drug Saf 2006; 15: 618–27.

9 Jara-Oseguera A, Simon SA, Rosenbaum T. TRPV1: on the road to pain relief. Curr Mol Pharmacol 2008; 1: 255–69.

10 Szallasi A, Cortright DN, Blum CA, Eid SR. The vanilloid receptor TRPV1: 10 years from channel cloning to antagonist proof-of-concept. Nat Rev Drug Discov 2007; 6: 357–72.

11 Gomtsyan A, Bayburt EK, Schmidt RG, Surowy CS, Honore P, Marsh KC, Hannick SM, McDonald HA, Wetter JM, Sullivan JP, Jarvis MF, Faltynek CR, Lee CH. Identification of (R)-1-(5-tert-butyl-2,3-dihydro-1H-inden-1-yl)-3-(1H-indazol-4-yl)urea (ABT-102) as a potent TRPV1 antagonist for pain management. J Med Chem 2008; 51: 392–5.

12 Surowy CS, Neelands TR, Bianchi BR, McGaraughty S, El Kouhen R, Han P, Chu KL, McDonald HA, Vos M, Niforatos W, Bayburt EK, Gomtsyan A, Lee CH, Honore P, Sullivan JP, Jarvis MF, Faltynek CR. (R)-(5-tert-butyl-2,3-dihydro-1H-inden-1-yl)-3-(1H-indazol-4-yl)-urea (ABT-102) blocks polymodal activation of transient receptor potential vanilloid 1 receptors *in vitro* and heat-evoked firing of spinal dorsal horn neurons *in vivo*. J Pharmacol Exp Ther 2008; 326: 879–88.

13 Honore P, Chandran P, Hernandez G, Gauvin DM, Mikusa JP, Zhong C, Joshi SK, Ghilardi JR, Sevcik MA, Fryer RM, Segreti JA, Banfor PN, Marsh K, Neelands T, Bayburt E, Daanen JF, Gomtsyan A, Lee CH, Kort ME, Reilly RM, Surowy CS, Kym PR, Mantyh PW, Sullivan JP, Jarvis MF, Faltynek CR. Repeated dosing of ABT-102, a potent and selective TRPV1 antagonist,

enhances TRPV1-mediated analgesic activity in rodents, but attenuates antagonist-induced hyperthermia. Pain 2009; 142: 27–35.

14 Bromm B, Jahnke MT, Treede RD. Responses of human cutaneous afferents to CO_2 laser stimuli causing pain. Exp Brain Res 1984; 55: 158–66.

15 Schaffler K, Wauschkuhn CH, Brunnauer H, Rehn D. Evaluation of the local anaesthetic activity of dimetindene maleate by means of laser algesimetry in healthy volunteers. Arzneimittelforschung 1992; 42: 1332–5.

16 Schaffler K, Wauschkuhn CH, Gierend M. Analgesic potency of a new anticonvulsant drug versus acetylsalicylic acid via laser somatosensory evoked potentials. Randomized placebo-controlled double-blind (5-way) crossover study. Arzneimittelforschung 1991; 41: 427–35.

17 Chizh BA, Priestley T, Rowbotham M, Schaffler K. Predicting therapeutic efficacy - experimental pain in human subjects. Brain Res Rev 2009; 60: 243–54.

18 Alexander SPH, Mathie A, Peters JA. Guide to Receptors and Channels (GRAC), 5th edition. Br J Pharmacol 2011; 164: (Suppl. 1): S1–S324.

19 Othman AA, Nothaft W, Awni WM, Dutta S. Pharmacokinetics of the TRPV1 antagonist ABT-102 in healthy human volunteers: population analysis of data from 3 phase 1 trials. J Clin Pharmacol 2011; 52: 1028–41.

20 Rowbotham MC, Nothaft W, Duan WR, Wang Y, Faltynek C, McGaraughty S, Chu KL, Svensson P. Oral and cutaneous thermosensory profile of selective TRPV1 inhibition by ABT-102 in a randomized healthy volunteer trial. Pain 2011; 152: 1192–200.

21 Jones B, Kenward M. Design and Analysis of Cross-over Trials. London: Chapman & Hall/CRC, 2003.

22 Abbott Nutrition. Ensure plus ingredients [online]. Updated 2011. Available at http://abbottnutrition.com/products/ensure-plus (last accessed 9 December 2011).

23 Othman AA, Cheskin H, Locke C, Nothaft W, Dutta S. A phase 1 study to evaluate the bioavailability and food effect of twosolid-dispersion formulations of the TRPV1 antagonist ABT-102, relative to the oral solution formulation, in healthy human volunteers. Clin Pharmacol Drug Dev 2012; 1: 24–31.

24 Xu RN, Vaca P, Rieser MJ, El-Shourbagy TA. Highly sensitive LC-MS-MS analysis of a pharmaceutical compound in human plasma using monolithic phase-based on-line extraction. J Chromatogr Sci 2009; 47: 473–7.

25 International Federation of Pharmaceutical Manufacturers and Associations. 2007 Medical Dictionary for Regulatory Activities, Version 10.1. In. VAR1/8A/MSSO ed. 12011 Sunset Hills Rd., Reston VA 20190-3285, USA: MedDRA Maintenance and Support Services Organization.

26 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.

27 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.

28 Liao S, Hill J, Nayak R. Pharmacokinetics of tramadol following single and multiple doses in man. Pharm Res 1992; 9: 308

29 Agrawal ng, Porras AG, Matthews CZ, Rose MJ, Woolf EJ, Musser BJ, Dynder AL, Mazina KE, Lasseter KC, Hunt TL, Schwartz JI, McCrea JB, Gottesdiener KM. Single- and multiple-dose pharmacokinetics of etoricoxib, a selective inhibitor of cyclooxygenase-2, in man. J Clin Pharmacol 2003; 43: 268–76.

30 Carmon A, Dotan Y, Sarne Y. Correlation of subjective pain experience with cerebral evoked responses to noxious thermal stimulations. Exp Brain Res 1978; 33: 445–53.

31 Carmon A, Friedman Y, Coger R, Kenton B. Single trial analysis of evoked potentials to noxious thermal stimulation in man. Pain 1980; 8: 21–32.

32 Hoffmann RT, Schmelz M. Time course of UVA- and UVB-induced inflammation and hyperalgesia in human skin. Eur J Pain 1999; 3: 131–9.

33 Bickel A, Dorfs S, Schmelz M, Forster C, Uhl W, Handwerker HO. Effects of antihyperalgesic drugs on experimentally induced hyperalgesia in man. Pain 1998; 76: 317–25.

34 Lee YM, Kim YK, Chung JH. Increased expression of TRPV1 channel in intrinsically aged and photoaged human skin *in vivo*. Exp Dermatol 2009; 18: 431–6.

35 Schaffler K. Proof of efficacy and dose-dependency of NSAID and opiate analgesics in Laser evoked potential paradigm - using capsaicin and UV skin model. Spring Pain Conference; 2008 April 26-May 3, 2008; Grand Cayman Island, British West Indies.

36 Crutchlow M, Dong Y, Schulz V, Hoydonck PV, Laethem T, Maes A, Larson P, Eid S, Kane S, Hans G, Murphy G, Chodakewitz J, Greenspan J, Blanchard R. Pharmacologic inhibition of TRPV1 impairs sensation of potentially injurious heat in healthy subjects. 110th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics; March 18-21, 2009; National Harbor, MD; Abstract LB-II-A-3.

37 Sugiura T, Tominaga M, Katsuya H, Mizumura K. Bradykinin lowers the threshold temperature for heat activation of vanilloid receptor 1. J Neurophysiol 2002; 88: 544–8.

38 Reeh PW, Petho G. Nociceptor excitation by thermal sensitization–a hypothesis. Prog Brain Res 2000; 129: 39–50.

39 Kichko TI, Reeh PW. TRPV1 controls acid- and heat-induced calcitonin gene-related peptide release and sensitization by bradykinin in the isolated mouse trachea. Eur J Neurosci 2009; 29: 1896–904.

40 Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, Schacht AL. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov 2010; 9: 203–14.