Effects of a Novel TRPV1 Antagonist ABT-102 in a Human Experimental Pain Study Using Laser Somatosensory Evoked Potentials Obtained from UV_B-irritated and Normal Skin in Healthy Volunteers

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Abstract

Laser induced nociceptive stimulation is a well-accepted and validated method in experimental human pharmacology to measure analgesia in an objective quantitative manner.

The primary objective of this study was to compare the analgesic efficacy (Peak-to-Peak / PtP Laser somatosensory evoked potentials / LSEP amplitude reduction in Vertex EEG) of the novel TRPV1 antagonist ABT-102 vs. tramadol, etoricoxib as active controls and placebo in UV_B-irritated skin. ABT-102 has shown robust efficacy in diverse preclinical pain models.

This was a randomized, placebo-controlled, double-blind, single center, intra-individual crossover trial. Twenty-four eligible healthy male subjects were randomly assigned to receive 6 different sequences of single oral doses of ABT-102 (0.5, 2, 6 mg), etoricoxib (90 mg), tramadol (100 mg) and placebo to treat mild to moderate pain induced by CO_2 laser on normal (analgesia) and on UV_B-irritated (anti-hyperalgesia) skin. LSEPs from both skin types were taken at baseline and each hour up to 8 hours post-dose.

For LSEP PtP amplitude (primary variable), statistically significant reductions in the post-dose average over the 8-hour period on UV_B skin vs. placebo were observed with tramadol 100 mg and etoricoxib 90 mg (P<0.001, P=0.001) and for ABT-102 6 and 2 mg (P<0.001, P=0.002). 0.5 mg ABT-102 showed an effect close to placebo, 2 mg ABT-102 was comparable to tramadol and etoricoxib. 6 mg ABT-102 was statistically superior to the reference compounds (P<0.05) over the 8-hour period with a peak effect consistent with the PK T_{max} at around 2-3 hours.

A similar LSEP pattern was observed on normal skin (6 mg of ABT-102 vs. placebo, P<0.001, and vs. active comparators, P<0.05). LSEP amplitude attenuations with 2 and 6 mg ABT-102 were of clinically relevant magnitude for both skin conditions. Consistent with LSEPs, ABT-102 resulted in a dose-dependent reduction in subjective pain VAS scores on UV_B-irritated and normal skin. 6 mg ABT-102 was superior to both placebo (P<0.001) and the active comparators (P<0.005) on UV_B skin and on normal skin. Core body temperature remained below 39°C in all subjects. There were no other relevant safety findings.

Simultaneous measurements of LSEP amplitudes and VAS pain scores were performed to quantify the analgesic efficacy of ABT-102. The effect of 6 mg ABT-102 was statistically superior to tramadol and etoricoxib for the reduction of PtP LSEP amplitudes and VAS pain scores. 2 mg was comparable to both active controls. Interestingly, for both 6 mg ABT-102 and 2 mg ABT-102, the LSEP amplitude reductions on UV_B and normal skin were similar. It remains to be determined how these promising results may translate into a clinical effect in patients with chronic pain.

Introduction

- One of the greatest unmet needs in pain management exists in the treatment of moderate to severe chronic nociceptive pain.[1]
- Transient receptor potential vanilloid type 1 (TRPV1) receptors are activated in association with inflammation that occurs in both acute and chronic nociceptive pain.[2]
- ABT-102 is a TRPV1 channel antagonist, representing a novel mechanism of action for the treatment of nociceptive pain.[3, 4]
- ABT-102 has shown efficacy in pre-clinical models of acute and chronic nociceptive pain of both cancer and non-cancer etiology.[5]

Objective

The primary objective of this study was to compare the efficacy of single doses of ABT-102 (0.5, 2, and 6 mg), tramadol (100 mg), and etoricoxib (90 mg) to placebo in subjects with experimentally-induced mild to moderate pain.

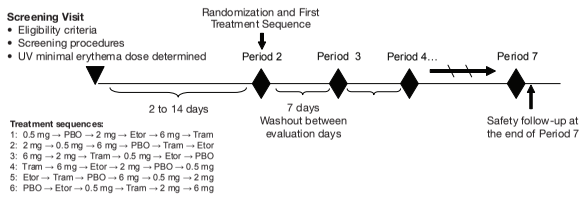
Methods

Study Design

- This was a phase 1, single-dose, randomized, double-blind, placebo and active-controlled, six-period, intra-individual complete crossover, single center study in 24 healthy male subjects.
- The trial was conducted in accordance with ICH GCP guidelines.
- The study was originally planned to evaluate higher dose levels of ABT-102. However, due to a finding in a concurrent toxicology study, the dose levels were revised to 0.5, 2, and 6 mg to maintain appropriate safety margins. As very limited data were generated before the dose levels were revised, only the findings for the lower dose levels will be described and discussed.
- The study received ethics committee approval and informed consent was obtained from all participants prior to any study procedures.

Methods (cont.)

Figure 1. Study Design



Subjects

Twenty-four eligible healthy subjects were to be enrolled in the study. Key eligibility criteria were as follows:

- Males ≥18 and ≤60 years in general good health.
- No wide-spread acne, tattoos, or scars at the sites for UV and laser exposures on the back.
- Subjects who had used investigational drugs or drugs that induce CYP3A4 within one month of study drug administration, required the use of regular medications, or those with any clinically significant laboratory result, ECG finding, medical history, or current medical condition were excluded from the study.
- 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

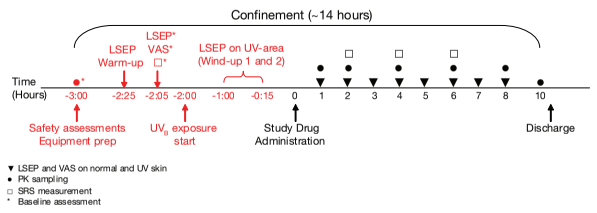
- UV_B irradiation was applied at the Screening visit in ascending doses (corresponding to different irradiation times) to 6 different small areas of skin on the back to determine the individual minimum UV_B dose that produced the first clearly discernible erythema.
- Eligible subjects were randomized to receive one of 6 different sequences of blinded, single doses of ABT-102 (0.5, 2, and 6 mg), etoricoxib 90 mg, tramadol 100 mg, and placebo (intra-individual crossover).
- Pain was induced by repeated CO_2 laser stimuli to normal skin and to UV_B-irritated skin (similar to sunburn)
  - The 2-fold individual minimal erythema dose (MED) of UV_B was applied 2 hours prior to study drug administration to skin on the back to produce a homogeneous area of skin erythema and hyperalgesia.
  - The UV_B-treated area was large enough (5x5 cm) to perform repeated measurements per assessment day.
  - A painful CO_2-laser stimulus was applied to normal and UV_B-treated areas at the times indicated.
  - Two "wind-up" (kindling) sessions on UV_B-treated skin were performed prior to study drug administration to enhance hyperalgesia development.
  - The skin areas were randomly switched in each medication period; UV exposure was always contra-lateral to the normal skin condition.
  - The normal skin evaluation was always performed first in each drug assessment sequence.

Assessments

Assessments and pharmacokinetic sampling in relation to study drug dosing are illustrated in Figure 2.

- Pain intensity was measured via:
  - Laser somatosensory evoked potentials (LSEP) from Vertex-EEG as peak-to-peak (PtP) amplitude, a neurophysiologic measure of brain cell activity in pain perception.
  - A visual analog scale (VAS), a self-reported paper and pencil measure of perceived pain. The VAS was completed by the subjects immediately after each LSEP session.
- UV-erythema intensity was measured by Skin Reflection Spectrometry (SRS) to evaluate the anti-inflammatory effect of ABT-102, tramadol, and etoricoxib.

Figure 2. Study Assessments (Periods 2 through 7)



Methods (cont.)

Statistical Methods

Efficacy

- The primary efficacy variable was the averaged (artifact-free) LSEP PtP amplitude from Vertex-EEG leads after repeated CO_2 laser stimulation of UV_B-irritated skin.
- Secondary efficacy variables included:
  - LSEP PtP amplitude on repeated CO_2 laser stimulation of normal skin
  - VAS pain scores on repeated CO_2 laser stimulation of both skin types
  - SRS evaluation of UV_B-irradiated area
- For LSEP, VAS, and SRS variables, a linear mixed effects model for the analysis of a repeated measures cross-over design 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 regimen 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 LSEP and VAS variables, within the framework of the model, the hypothesis no interaction between tramadol and placebo with time of measurement was tested at significance level 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, tests for other pair-wise comparisons of treatments were performed.

Safety

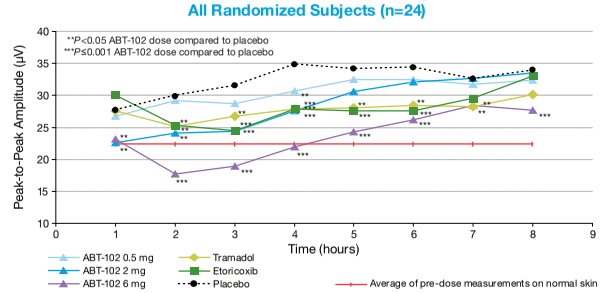
- Adverse events were coded using MedDRA[6] and were tabulated by System Organ Class and MedDRA preferred term with a breakdown by treatment.
- Laboratory test values, vital sign measurements, and ECG interval values that were potentially clinically significant according to predefined criteria were identified and listed separately.
- A linear mixed effects model like that described for the LSEP 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

All 24 subjects were white males with a mean age of 38.1 years; all completed the study.

Results for the primary efficacy variable (on hyperalgesic UV_B skin) over time are presented in Figure 3.

Figure 3. LSEP PtP Amplitude over Time in UV_B-Irritated Skin, All Randomized Subjects (n=24)

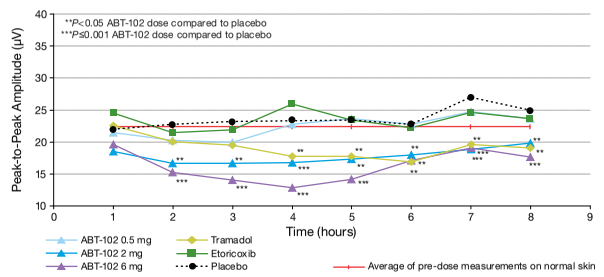


- PtP amplitude increased over time with placebo when CO_2 laser stimulated UV_B-irritated skin was assessed (hyperalgesia development in UV skin vs. normal skin at baseline).
- Statistically significant reductions compared to placebo were observed with ABT-102 6 mg (P<0.001), ABT-102 2 mg (P=0.002), tramadol 100 mg (P<0.001), and etoricoxib 90 mg (P=0.001) for the average post-administration (p.a.) reduction over 8 hours.
- ABT-102 6 mg was statistically significantly more effective than placebo in reducing PtP amplitude at all p.a. time points from 1 to 8 hours (P<0.05).
- The peak effect of ABT-102 6 mg occurred at 2-3 hours, consistent with T_{max} seen in PK measurements.
- ABT-102 6 mg also demonstrated statistical superiority to both active comparators 1 to 4 hours post-dose and to etoricoxib at 8 hours (P<0.05).
- Treatment with 2 mg ABT-102 was comparable to the active comparators.
- ABT-102 0.5 mg was close to the effects observed with placebo.

Results (cont.)

LSEP PtP results over time on normal (non-hyperalgesic) skin are presented in Figure 4.

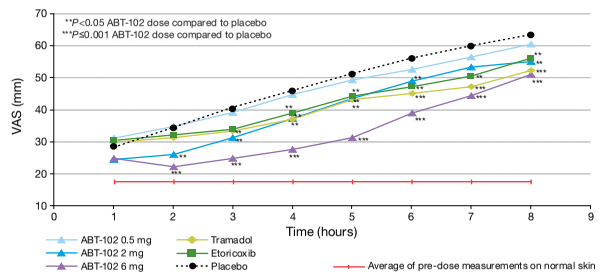
Figure 4. LSEP PtP Amplitude over Time in Normal Skin, All Randomized Subjects (n=24)



- In contrast to UV_B-irradiated skin, no relevant hyperalgesic development (increase) could be observed in PtP amplitude in normal skin after repeated laser stimulation over the assessment day vs. baseline values (see placebo values).
- Both ABT-102 6 mg and 2 mg demonstrated a statistically significant reduction in PtP amplitude compared to placebo (P<0.001 for the average reduction over 8 hours at both doses).
- ABT-102 6 mg was statistically significantly more effective compared to both tramadol 100 mg (P<0.05) and etoricoxib 90 mg (P<0.001) for the average PtP p.a. reduction over 8 hours.
- Tramadol was statistically significantly better compared to placebo (P<0.001 for the average reduction over 8 hours).
- Etoricoxib 90 mg exhibited a placebo-like effect on normal skin for the average p.a. reduction over 8 hours.
- The effect of ABT-102 0.5 mg was similar to that of placebo.

The pain VAS scores increased with repeated CO_2 laser stimulation of both normal and UV_B-irritated skin. VAS results on UV_B-irritated (hyperalgesic) skin are presented in Figure 5.

Figure 5. Pain VAS Scores over Time in UV_B-Irritated Skin, All Randomized Subjects (n=24)

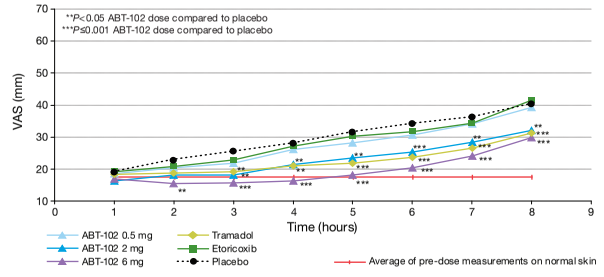


- ABT-102 6 mg and 2 mg showed statistically significant improvements in pain VAS scores compared with placebo (P<0.001 and P=0.002, respectively) for the average p.a. reduction over 8 hours.
- ABT-102 6 mg demonstrated a statistically significant decrease in pain VAS score compared with tramadol 100 mg (P=0.005) and etoricoxib 90 mg (P<0.001) for the average p.a. reduction over 8 hours.
- A statistically significant decrease was observed with both tramadol 100 mg (P=0.002) and etoricoxib 90 mg (P=0.019) compared with placebo for the average p.a. reduction over 8 hours.
- ABT-102 2 mg was comparable to the active controls.
- The effect of ABT-102 0.5 mg was similar to that of placebo.

Results (cont.)

VAS results over time on normal (non-hyperalgesic) skin are presented in Figure 6.

Figure 6. Pain VAS Scores over Time in Normal Skin, All Randomized Subjects (n=24)



- ABT-102 6 mg and 2 mg showed statistically significant improvement compared with placebo (P<0.001 for both doses) for the average p.a. reduction over 8 hours.
- ABT-102 6 mg was numerically better at all time points than tramadol 100 mg and statistically significantly better than etoricoxib (P<0.001) for the average p.a. reduction over 8 hours.
- ABT-102 2 mg was comparable to tramadol 100 mg and the average difference in VAS pain scores was statistically significant compared with etoricoxib 90 mg.
- The effect of ABT-102 0.5 mg was similar to the effects of placebo and etoricoxib.

UV-Erythema Intensity Measurement by SRS

- When compared with placebo, all doses of ABT-102 and tramadol demonstrated negligible effects on UV-erythema intensity by SRS measurement.
- Etoricoxib was the only treatment that showed a statistically significant effect compared with placebo (P=0.001 for the average p.a. reduction over 6 hours), as a result of its anti-inflammatory effect.

Concurrent Pharmacokinetic Results

- The PK profile was consistent with results obtained from earlier single-dose studies of ABT-102.
- T_{max} was observed at approximately 2 hours.
- Exposure levels appeared to increase in a dose linear fashion.

Safety and Tolerability

- There were no serious adverse events and all treatment-emergent adverse events were mild in severity.
- The most frequently reported adverse event in subjects taking ABT-102 was feeling cold, reported by 10 subjects (41.7%) in the 6 mg group and 6 subjects (25%) in the 2 mg group.
- Core body temperature remained below 39°C (102.2°F) in all subjects.
- There were no clinically significant safety findings and ABT-102 was generally well tolerated.

Conclusions

- ABT-102 6 mg and 2 mg were effective in reducing experimentally-induced pain in normal human subjects as assessed by LSEP PtP amplitude from subjects with repeated CO_2 laser stimulation of UV_B-irritated (hyperalgesic) skin.
- ABT-102 exhibited dose-dependent effects vs. placebo in normal and UV_B-irritated skin.
- ABT-102 6 mg and 2 mg showed statistically significant improvements in pain VAS scores compared with placebo in both normal and UV_B-irritated skin.
- ABT-102 was safe and well tolerated in this 6-period crossover study.
- The clinical effects of ABT-102 in the management of chronic pain remain an area for further investigation.

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