Biased agonism of the μ-opioid receptor by TRV130 increases analgesia and reduces on-target adverse effects versus morphine: A randomized, double-blind, placebo-controlled, crossover study in healthy volunteers

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

Keywords:
mu-Opioid receptor
Biased ligand
Clinical trial
Morphine
Postoperative pain

ARTICLE INFO

Article history:
Received 19 March 2014
Received in revised form 13 June 2014
Accepted 16 June 2014

Keywords:
mu-Opioid receptor
Biased ligand
Clinical trial
Morphine
Postoperative pain

ABSTRACT

Opioids provide powerful analgesia but also efficacy-limiting adverse effects, including severe nausea, vomiting, and respiratory depression, by activating μ-opioid receptors. Preclinical models suggest that differential activation of signaling pathways downstream of these receptors dissociates analgesia from adverse effects; however, this has not yet translated to a treatment with an improved therapeutic index. Thirty healthy men received single intravenous injections of the biased ligand TRV130 (1.5, 3, or 4.5 mg), placebo, or morphine (10 mg) in a randomized, double-blind, crossover study. Primary objectives were to measure safety and tolerability (adverse events, vital signs, electrocardiography, clinical laboratory values), and analgesia (cold pain test) versus placebo. Other measures included respiratory drive (minute volume after induced hypercapnia), subjective drug effects, and pharmacokinetics. Compared to morphine, TRV130 (3, 4.5 mg) elicited higher peak analgesia (105, 116 seconds latency vs 75 seconds for morphine, \(P < .02\)), with faster onset and similar duration of action. More subjects doubled latency or achieved maximum latency (180 seconds) with TRV130 (3, 4.5 mg). Respiratory drive reduction was greater after morphine than any TRV130 dose (\(\text{C}0 \times 15.9\) for morphine versus \(\text{C}0 \times 7.3, 7.6, \) and \(9.4 \times L/\text{min}, P < .05\)). More subjects experienced severe nausea after morphine (n = 7) than TRV130 1.5 or 3 mg (n = 0, 1), but not 4.5 mg (n = 9). TRV130 was generally well tolerated, and exposure was dose proportional. Thus, in this study, TRV130 produced greater analgesia than morphine at doses with less reduction in respiratory drive and less severe nausea. This demonstrates early clinical translation of ligand bias as an important new concept in receptor-targeted pharmacotherapy.

1. Introduction

Conventional opioids provide powerful analgesia in the acute pain setting, but also produce efficacy-limiting adverse effects, such as severe nausea, vomiting and potentially life-threatening respiratory depression [3,20,24,32]. Both analgesia and adverse effects of conventional opioids are mediated by the μ-opioid receptor, leading to the assumption that these effects are inseparable [13]. Previous opioid development reflected this; pharmacological innovation was limited to the discovery of partial agonists such as buprenorphine, peripherally restricted antagonists such as methylnaltrexone and alvimopan, and multi-target drugs such as tapentadol [6,23,27,28]. These agents added important options for the management of pain but have not solved key drawbacks of opioid pharmacology, leaving important unmet needs in pain treatment. To date, dissociation of centrally mediated analgesia from centrally mediated adverse events such as respiratory depression and nausea has not been possible.

In mice with targeted genetic deletion or siRNA ablation of the receptor-coupling scaffold protein β-arrestin2, morphine displayed increased analgesia [4,15] but less respiratory depression and constipation compared to wild-type mice [21]. It was hypothesized

http://dx.doi.org/10.1016/j.pain.2014.06.011
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that this pharmacology could be recapitulated by “biased ligands,” a recently discovered class of receptor ligands that, unlike full or partial agonists, selectively engage a subset of normal receptor responses [12,30]. In particular, biased ligands can discriminatively engage G protein coupling, the canonical receptor signaling mechanism, or β-arrestins, a more recently elucidated mechanism of receptor signal transduction [7]. Biased ligands produce differentiated pharmacology in preclinical studies compared to unbiased ligands [1,29], but this concept has not yet been tested in humans.

To determine whether differential activation of μ-opioid pathways dissociates analgesia from adverse effects, we discovered TRV130, a “G protein-biased” μ-opioid ligand with G protein–coupling efficacy similar to that of morphine, but markedly reduced receptor phosphorylation, engagement of β-arrestin2, and internalization [5,8]. As predicted, this profile translated into robust analgesia with reduced respiratory and gastrointestinal dysfunction in rodents (Fig. 1). Based on these findings, TRV130 was progressed to clinical development to test whether G protein–biased μ-opioid ligands might offer improved therapeutic profiles compared to currently prescribed opioid analgesics. The current study evaluated TRV130 versus placebo and morphine in an evoked pain model in healthy volunteers. The study incorporated hypercapnic ventilatory response testing and a quantitative drug effects questionnaire, as well as safety, tolerability, and pharmacokinetic measures, to model therapeutic index as an early assessment clinical differentiation from morphine.

The primary objectives were to evaluate the safety and tolerability of intravenous TRV130, as measured by adverse events, vital signs, physical examinations, electrocardiography, and clinical laboratory values, and to evaluate the analgesic effect of TRV130 versus placebo using the cold pain test (CPT), as measured by hand removal latency.

The secondary objectives were to evaluate the analgesic effect of TRV130 versus morphine using the CPT; the effect of TRV130 on the ventilatory response to hypercapnia (VRH), as measured by the ratio of minute ventilation over end-tidal CO2; and the pharmacokinetics of TRV130. The exploratory objective was to evaluate the effect of TRV130 on responses to the Drug Effect Questionnaire (DEQ), including an assessment of nausea.

2. Methods

2.1. Study design

This study was a single-center (CRI Lifetree Inc, Salt Lake City, UT), randomized, double-blind, placebo-controlled, 5-period, crossover study conducted between July and September 2013 under the principles of the Declaration of Helsinki, International Conference on Harmonization of Good Clinical Practice guidelines, and applicable regulatory requirements. The protocol, informed consent and other relevant documentation were approved by New England Institutional Review Board (Newton, MA).

The TRV130 doses studied (1.5, 3, and 4.5 mg) spanned the expected pharmacodynamically active range, based on pupillometry data from earlier trials [25]. The dose of morphine (10 mg) has been extensively used as a benchmark in experimental pain and was expected to produce a robust increase in hand removal latency in the CPT [9,26]. Placebo was 5% dextrose in water. A single cohort of 30 individuals was selected as likely to give statistically significant effects of the morphine comparator based on past experience of the investigator.

The subjects were healthy male volunteers aged 18 to 50 years, with body mass indices of 19.0 to 32.0 kg/m2. Given the differential response to opioids, females were not included [6,9,16]. To ensure adequate subject test sensitivity and reliability, subjects were required to have repeated screening CPT hand removal latencies of >20 and <120 seconds. Subjects were excluded if their medical history, examination, vital signs, oxygen saturation, or clinical laboratory results were indicative of any clinically significant illness, including active dermatological or ophthalmic conditions that could confound CPT or pupillometry testing, respectively. Clinically significant electrocardiographic abnormalities, including QTcF ≥ 450 milliseconds, were exclusionary, as was positive serology for hepatitis B or C, or human immunodeficiency virus. A screening history of tobacco- or nicotine-containing product use (within 6 months), prescription, investigational or illegal drug use (within 35 days before screening), alcohol or over-the-counter medication use (within 72 hours before day 1) or recent (within 6 months) drug or alcohol abuse were exclusionary. A positive urine drug screen, urine cotinine test, or alcohol breath test at screening or check-in excluded the subject from participation. A screening history of blood product receipt (within 6 months) drug or alcohol abuse were exclusionary. A positive urine drug screen, urine cotinine test, or alcohol breath test at screening or check-in excluded the subject from participation. A screening history of blood product receipt (within 6 months) or donation (within 35 days before screening) were exclusionary. Subjects were required to refrain from drug, alcohol, and tobacco use during study participation and to refrain from sexual intercourse with pregnant or lactating women, women of child-bearing potential without contraception, or sperm donation through study participation and to refrain from sexual intercourse with pregnant or lactating women, women of child-bearing potential without contraception, or sperm donation through 90 days after last study medication administration.

During the 11-day/10-night sequestration, subjects randomly received single doses of TRV130, placebo, or morphine intravenously on days 1, 3, 5, 7, and 9 with assessments at baseline and...
at multiple timepoints postdose. Follow-up occurred approximately 7 days after the last dosing period.

The sponsor personnel, statistical consultant, investigator, clinical research associate, data manager, project manager, and subjects were kept blinded until an interim assessment after 10 subjects to qualitatively assess sample size, and then blinded again until the end of the study. A randomization schedule (block size of 10) was generated by the statistics, programming, and data management group at ICON plc (Hanover, MD) and transferred to an unblinded pharmacist at the study site, who prepared the investigational product into identical syringes for delivery to the blinded investigator and study staff. The order of treatments was not known or determined by the subject, investigator or study staff.

2.2. Pharmacodynamics

The CPT used a continuous circulating water bath (Model RW-1025G, Jeo Tech, Seoul Korea) held at 2.0 ± 0.05°C. The hand removal latency (pain tolerance) and time to first perceptible pain (pain threshold) (Grach 2004) were measured by stopwatch; pain intensity at hand removal (11-point numeric pain rating scale) and hand temperature (infrared thermometer to palm of tested hand) were also measured. The maximum allowable time of hand immersion was 180 seconds. Assessments were made predose and postdose at 10 and 30 minutes and at 1, 2, 3, 4, and 8 hours.

VRH testing was performed with the subject breathing through a facemask. A gas-mixing rebreathing apparatus delivered oxygen (95%) and CO₂ (5%) to a 100-L nondiffusing reservoir bag for breathing at normal pressures. For each test, the subject breathed this hypercapnic gas mixture for 5 minutes (procedure terminated if end-tidal CO₂ was ≥60 mm Hg for 3 consecutive breaths). Minute ventilation (expired minute volume), respiratory rate, flow rates (peak expired flow) and tidal volume (expired tidal volume) were also measured. Assessments were made predose and postdose at 10 minutes and at 1, 2, 3, 4, and 24 hours.

2.3. Tolerability

Subjects were instructed to report adverse events spontaneously. In addition, at numerous set time points throughout the study, the subjects’ experience of any adverse events were captured by open-ended questions (eg, “Have you noticed any change in your health?” or “How do you feel?”). Tolerability was also measured by periodic assessments of vital signs, physical examinations, electrocardiography, oxygen saturation, and clinical laboratory values.

2.4. Pharmacokinetics

Pharmacokinetic samples were collected for plasma concentration analyses of TRV130, morphine, and morphine 6-glucuronide for 24 hours after drug administration.

2.5. Statistical analyses

Primary comparisons of CPT were between TRV130 and placebo; comparisons between doses of TRV130 and morphine were exploratory. Analyses focused on point estimation and estimates of precision. P values were not adjusted for multiple comparisons. Descriptive statistics (eg, geometric mean) were also derived. Pharmacodynamic analyses were performed on the safety population, defined as all randomized subjects who received at least 1 dose of study drug.

Hand removal latency change from baseline was analyzed using the pairwise Wilcoxon signed rank test, and Hodges Lehmann estimates of medians and interquartile ranges (IQRs) were reported. Sequence, period and carry-over effect were evaluated by descriptive statistics. Pairwise Wilcoxon signed rank test was also used to analyze the area under the curve (AUC) for each DEQ item. Responder analyses were summarized descriptively as the number of subjects who doubled latency from baseline at least once, or achieved the CPT cutoff time at least once.

VRH was assessed by averaging the minute volume in the fifth minute of hypercapnic exposure at each timepoint. Change from baseline was analyzed using mixed models repeated measures assuming Kenward-Rogers degrees of freedom and an unstructured covariance matrix. The model included subject within time as a random effect, time as a repeated effect (blocked by subject within period), treatment and time as fixed effects, and treatment-by-time as a fixed interaction term. Carry-over effect was assessed by descriptive statistics. AUC of change from baseline was analyzed by mixed models methods including a term for subject as a random effect and treatment as a fixed effect. Responders were defined as change from baseline that exceeded the average placebo response plus 1 standard deviation, and were analyzed descriptively as the number and percentage responding by treatment group.

3. Results

3.1. Disposition

Of 30 subjects randomized, 29 completed the study (Supplementary Fig. 1). One subject electively discontinued for reasons unrelated to an adverse event or study procedures after completing all but the final dosing session (TRV130 1.5 mg). One subject experienced sustained moderate vomiting after receiving morphine and was unable to complete pharmacodynamic assessments but remained in the study. The subject mean age (SD) was 26.9 (5.76) years. Three subjects reported ethnicity as “Hispanic or Latino”; 1 subject reported race as “black or African American.”

3.2. Pharmacodynamics

TRV130 at all doses elicited a rapid and significant increase in CPT hand removal latency from baseline compared to placebo (Fig. 2A), with peak efficacy at the first measurement 10 minutes postdose (geometric means of 81, 106, and 116 seconds latency for TRV130 at 1.5, 3, and 4.5 mg, vs 41 seconds for placebo; P < .0001). TRV130 significantly increased hand removal latency for 2 to 3 hours compared to placebo at the 3- and 4.5-mg doses (P < .02), and for 1 hour at the 1.5-mg dose (P < .007). TRV130 at 3 and 4.5 mg also significantly (P < .02; P < .005) increased hand removal latency compared to morphine at 10 and 30 minutes, after which latency was similar to morphine. There was no evidence of a sequence, period, or carry-over effect; as anticipated, there was a near absence of a response after placebo administration on the CPT.

Consistent with the increased hand removal latency of TRV130, more subjects responded after TRV130, defined as a doubling of latency on at least 1 CPT; than after morphine (Fig. 2B). More subjects achieved the CPT cutoff time of 180 seconds after the 3- and 4.5-mg doses of TRV130 than after morphine, suggesting that the increased efficacy of TRV130 over morphine may be underestimated at these doses because of the testing convention (Fig. 2C). In all cases, time to first perceptible pain was similar to hand removal latency (data not shown).
TRV130 produced a transient reduction in respiratory drive at all doses tested (Fig. 3A), as measured by the change from baseline in minute volume in the fifth minute of hypercapnic exposure ($P < .02$ vs placebo for the first hour for TRV130 1.5 mg and for the first 2 hours at 3 and 4.5 mg). The reduction in respiratory drive after morphine was similar in magnitude to the peak effect of TRV130 at 30 minutes; however, unlike the transitory effect of TRV130, the effect of morphine on respiratory drive persisted through the final VRH measurement at 4 hours postdose ($P < .0006$ vs placebo at all timepoints). The effect of morphine was significantly greater than TRV130 at 3 or 4.5 mg at hours 2 through 4 ($P < .01$). Total reduction in minute ventilation, measured as the area under the curve over 4 hours compared to placebo (Fig. 3B), was significantly less after all doses of TRV130 than after morphine ($-15.9 \pm 4.1 \text{L/min}$ for morphine vs $-7.3 \pm 4.1, -7.6$, and $-9.4$ for TRV130 1.5, 3, and 4.5 mg; $P < .01, P < .01$, and $P < .05$).

With reduction in respiratory drive assessed by response analysis (change from baseline > average placebo response plus 1 standard deviation), more subjects experienced reduction in respiratory drive after morphine (66%) than after TRV130 (21%, 37%, and 47% at 1.5, 3, and 4.5 mg) or placebo (10%). Similarly, a substantial fraction of subjects (39%) experienced a reduction in respiratory drive without a doubling CPT latency after morphine, compared to 7% to 13% after TRV130 and 10% after placebo (Fig. 3C).

TRV130 elicited dose-related changes in subjective CNS effects, as measured by the DEQ. In general, TRV130 at 3 mg and morphine produced similar DEQ CNS effect profiles, in the context of increased analgesia of TRV130 at 3 mg (Supplementary Fig. 2), suggesting a greater therapeutic index of TRV130 relative to morphine. As measured by the DEQ (Fig. 4), more subjects experienced severe nausea after morphine (7 subjects, including 1 subject with moderate vomiting for 45 minutes who was unable to complete the DEQ) than after TRV130 1.5 or 3 mg (0, 1 subject); TRV130 4.5 mg elicited severe total nausea with frequency similar to that of morphine. The DEQ “feeling sick” item revealed trends similar to those for the nausea item. Vomiting was not assessed in the DEQ.

3.3. Safety and tolerability

TRV130 was generally well tolerated, with reported adverse events consistent with action at the $\mu$-opioid receptor, including nausea, vomiting, dizziness, somnolence, pruritus/flushing, and headache (Table 1). These effects appeared to be dose-related, with TRV130 1.5 mg producing a low incidence of adverse effects and TRV130 3 mg producing a profile of adverse events similar to those of morphine; TRV130 4.5 mg had an overall profile of adverse events similar to that of morphine but a greater incidence of nausea, dizziness, pruritus, and headache. The greater frequency of reported vomiting events after morphine (20%) than for any dose of TRV130 (0%, 3.3%, and 3.3% for TRV130 1.5, 3, and 4.5 mg respectively) is consistent with the DEQ finding of more severe nausea after morphine than after any TRV130 dose, despite a similar prevalence of nausea by adverse event reporting.

3.4. Pharmacokinetics

Plasma concentrations of TRV130 peaked within 10 minutes of infusion and decreased in a biphasic manner, indicating rapid distribution followed by an elimination phase (Supplementary Fig. 3). Exposure to TRV130 was dose proportional with $AUC_{0-\infty}$ of 43, 82, and 122 ng $\cdot$ h/mL for 1.5, 3, and 4.5 mg TRV130. These doses were associated with peak plasma concentrations of 47, 76, and 119 ng/mL.

4. Discussion

Conventional opioids provide powerful analgesia but also efficacy-limiting adverse effects. In the postoperative setting, 50% of patients experience moderate to severe pain despite receiving opioids [2], likely due in part to dose-limiting adverse effects such as severe nausea, vomiting, and risk of respiratory depression [20,24,32]. These on-target effects are mediated by the $\mu$-opioid receptor; however, preclinical data have suggested that at least
compared to morphine (10 mg) and placebo on change in minute volume during the fifth of 5 minutes of inspired 5% CO₂, measured for 4 hours after intravenous bolus dosing for 28 to 30 subjects. "P < .05 vs placebo, and "P < .05 vs morphine by mixed-models repeated-measures analysis with unadjusted P values. (B) Total hypoventilation, the area under the placebo-corrected curve, for change in minute volume as in panel A. "P < .05 for TRV130 response less than morphine by mixed-models repeated-measures analysis with unadjusted P values. (C) Comparison of the percentage of subjects responding in the cold pain test (doubling of baseline latency at least once, solid bars) and the percentage of subjects exhibiting hypoventilation (change from baseline exceeding the average plus 1 standard deviation of the placebo response, hatched bars).

Fig. 4. Magnitude of nausea reported by subjects on a visual analog scale. The effect of TRV130 (1.5, 3, and 4.5 mg) compared to morphine (10 mg) and placebo, measured for 4 hours after intravenous bolus dosing for 28 to 30 subjects. Each datum represents a single subject, with median shown as a black line. *Subject experienced syncope and moderate vomiting, precluding pharmacodynamic measures; maximum nausea score was assumed.

can dissociate analgesia from CNS adverse effects, and none have been shown to increase analgesia [6,23,27,28]. Thus, a G protein-biased ligand such as TRV130 that increases analgesia and reduces β-arrestin-dependent adverse effects could be a substantial advance in opioid pharmacotherapy.

The current study of TRV130 is most relevant to postoperative pain, in which opioids are frequently administered by intravenous bolus. Inadequate treatment of pain in this setting, in addition to increasing patient discomfort, can prolong hospitalization, promote polypharmacy, increase co-morbidity, and potentiate the transition of acute pain to chronic pain [11]. However, adequate opioid doses may also produce adverse effects. Nausea and vomiting, polypharmacy, prolonged hospitalization due to delayed oral intake, and increased co-morbidity, ranging from dehydration to potentially life-threatening respiratory depression, all have an impact on patients’ recuperation and satisfaction with postoperative care [3,20,24,32]. This reflects the narrow therapeutic indices that limit utility of current opioids. Based on a mechanistic hypothesis postulating both increased analgesia and reduced adverse events for μ-opioid receptor activation in the absence of β-arrestin2 engagement, TRV130 is under investigation to increase the therapeutic index of opioid therapy. This study used experimental medicine methodologies to evaluate this hypothesis at an early stage of clinical development. Such translational medicine studies are important for elucidating key aspects of novel analgesics to investigate in later clinical development. The CPT, a well-validated model of opioid analgesia [14], indicated that TRV130 at 3 and 4.5 mg elicited improved analgesia compared to morphine 10 mg, with more rapid onset, superior analgesic effect, and similar duration of action compared with morphine. Mechanistically, opioid analgesia is associated with G protein coupling to the μ-opioid receptor [10]. Conventional opioids also stimulate β-arrestin coupling to the μ-opioid receptor, which hinders G protein coupling, thereby limiting analgesic effect [4,7]. Thus the failure of TRV130 to substantially engage β-arrestins “disinhibits” G-protein-mediated analgesia, potentially explaining the increased effect of TRV130 compared to morphine in the CPT. The rapid onset of
analgesia for TRV130 is consistent with rapid distribution of the molecule after bolus injection [25].

Opioids are well known to reduce the responsiveness of the respiratory centers to carbon dioxide, depressing the increased minute volume normally elicited by hypercapnia [31]. VRH testing indicated that the adverse respiratory effects of morphine may outlast analgesia, potentiating the risk of respiratory depression with successive dosing of morphine in an effort to maintain analgesia. This may explain why clinical respiratory depression is associated with cumulative morphine use and not simply maximum receptor occupancy.

In contrast, TRV130 produced less reduction in respiratory drive than morphine despite increased CPT efficacy. Although TRV130 produced a transient reduction at all doses tested, the reduction in respiratory drive after morphine was similar in magnitude but persisted through 4 hours postdose (the last time point measured), with more subjects experiencing a reduction in respiratory drive after morphine than after TRV130. The more benign profile of reduction in respiratory drive evidenced after TRV130 may translate to less co-morbidity (eg, atelectasis or risk of respiratory depression) in clinical care.

The DEQ nausea item revealed a higher frequency of severe nausea scores after morphine than after TRV130 1.5 and 3 mg. This was consistent with the increased number of subjects observed to vomit after morphine (6) than for any TRV130 dose (0, 1, and 4 for 1.5, 3, and 4.5 mg TRV130), and less consistent with the similar prevalence of nausea generated by adverse event reporting. This limitation of adverse event reporting is also evidenced after morphine, in which reports of vomiting (6) exceeded those of nausea (4). As an exploratory objective, these findings may represent early clinical evidence for potentially important differentiation of TRV130 from morphine. The reduced severity of nausea and vomiting elicited by TRV130 1.5 and 3 mg may lessen the delayed food intake and constipation associated with current opioids, and will be carefully measured in future studies of TRV130 using more refined assessment tools.

TRV130 elicited dose-related changes in a range of other subjective CNS effects, as measured by the DEQ. In general, TRV130 3 mg and morphine produced similar DEQ CNS effect profiles, despite increased CPT responses found for TRV130 3 mg. These findings suggest that the effects of a G protein–biased μ-opioid receptor ligand on CNS effects other than respiratory drive and nausea/vomiting may be less problematic in the context of increased analgesic efficacy.

Although limited by the use of healthy volunteers and by a small sample size, the experimental methodologies used in this study are well validated and useful for predicting efficacy and adverse effects in patients [9,14,16,18,19,22,26,31,33], enabling an early, multifactorial assessment of pharmacological differentiation with high likelihood of translatability to clinical development. This study suggests that TRV130 may have an improved therapeutic index, producing superior analgesia, less reduction in respiratory drive, and less severe nausea, compared with morphine. Larger studies of efficacy and tolerability of TRV130 compared with morphine in clinical pain will be required to confirm this possibility.

4.1. Conclusion

In conclusion, our findings demonstrate that TRV130, as a G protein–biased μ-opioid receptor ligand, can improve well-validated pharmacology in humans, as predicted from basic research and preclinical drug discovery studies. The dissociation of analgesic signals from respiratory and gastrointestinal signals by TRV130 seen in these experimental models suggests improved analgesic potential compared with that of morphine. This principle of improved on-target pharmacology may extend to biased opioid ligands for other pain indications and, more broadly, to other receptors and indications. Many G protein–coupled receptors (GPCRs) have been pursued as novel pain targets, but have failed to deliver new medicines, often limited by on-target adverse pharmacology. Thus the validation provided by this study may provide precedent for future discovery and development of biased ligands to deliver safer, more efficacious GPCR-targeted analgesics.

This study is registered on clinicaltrials.gov, number NCT02083315.

Conflict of interest statement

This study was sponsored by Trevena, Inc, King of Prussia, PA, which is developing TRV130 for the treatment of pain. Drs. Soergel, Subach, Lark, James, Skobieranda, and Violin were all employees of Trevena Inc during the planning, execution, and analysis of the study, and the writing of this manuscript. Dr. Burnham was an employee of Hambel Statistical Consulting, paid by Trevena Inc for work on this study. Dr. Sadler was an employee of ICON plc, paid by Trevena Inc for work on this study. Dr. Webster was an employee of CRI Lifetree Inc, paid by Trevena Inc for work on this study.

Acknowledgements

The authors thank all participating investigators and volunteers for their contributions to this study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2014.06.011.

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