A randomized, phase 2 study investigating TRV130, a biased ligand of the \( \mu \)-opioid receptor, for the intravenous treatment of acute pain

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Abstract

Efficacy of conventional opioids can be limited by adverse events (AEs). TRV130 is a structurally novel biased ligand of the \( \mu \)-opioid receptor that activates G protein signaling with little \( \beta \)-arrestin recruitment. In this phase 2, randomized, placebo- and active-controlled study, we investigated the efficacy and tolerability of TRV130 in acute pain after bunionectomy. We used an adaptive study design in which 144 patients experiencing moderate-to-severe acute pain after bunionectomy were randomized to receive double-blind TRV130, placebo, or morphine in a pilot phase. After pilot phase analysis, 195 patients were randomized to receive double-dummy TRV130 0.5, 1, 2, or 3 mg every 3 hours (q3h); placebo; or morphine 4 mg q4h intravenously. The primary end point was the time-weighted average change in numeric rating scale pain intensity over the 48-hour treatment period. Secondary end points included stopwatch and categorical assessments of pain relief. Safety and tolerability were also assessed. TRV130 2 and 3 mg q3h, and morphine 4 mg q4h produced statistically greater mean reductions in pain intensity than placebo over 48 hours \((P < 0.005)\). TRV130 at 2 and 3 mg produced significantly greater categorical pain relief than morphine \((P < 0.005)\) after the first dose, with meaningful pain relief occurring in under 5 minutes. TRV130 produced no serious AEs, with tolerability similar to morphine.

These results demonstrate that TRV130 rapidly produces profound analgesia in moderate-to-severe acute pain, suggesting that G-protein-biased \( \mu \)-opioid receptor activation is a promising target for development of novel analgesics.

Keywords: TRV130, Acute pain, Opioid, Biased ligand, Bunionectomy

1. Introduction

Acute pain management is clinically challenging, and patients commonly experience unrelied pain.\(^4\) As guidelines suggest, pain is often inadequately treated with a single pharmacologic agent because of the multifactorial nature of pain.\(^3,20\) Opioids are widely used to treat moderate-to-severe acute pain\(^3\) but are associated with opioid-related adverse events (ORAEs) such as respiratory depression, gastrointestinal effects (eg, nausea, vomiting, constipation) and sedation.\(^25,27,28\) These on-target adverse effects limit dosing to below what is required to deliver requisite analgesic efficacy and ultimately limit clinical utility (CU).\(^27\) Conventional opioids bind to the \( \mu \)-opioid receptor and activate signaling pathways to produce G-protein-mediated analgesia, but also recruit \( \beta \)-arrestin, which mediates receptor desensitization and internalization (Fig. 1).\(^8,17,29,33\) Studies in \( \beta \)-arrestin-2 knockout mice treated with morphine demonstrated that activation of G-protein signaling without concurrent \( \beta \)-arrestin recruitment resulted in enhanced analgesia while reducing respiratory and gastrointestinal effects compared with wild-type animals.\(^9,30,36\)

TRV130 is a G-protein-biased ligand of the \( \mu \)-opioid receptor: It produces G protein activation with little \( \beta \)-arrestin recruitment, presumably by changing the conformation of the \( \mu \)-opioid receptor when it binds, resulting in lessened \( \beta \)-arrestin recruitment, as has been observed in peptides that modulate other G-protein-coupled receptors.\(^36\) TRV130 has demonstrated potent analgesia and a differentiated tolerability profile in preclinical models, including less constipation and respiratory depression at equianalgesic doses.\(^13,18,33\) Experiments in vitro have found that TRV130 differs from morphine in receptor phosphorylation and internalization, as well as \( \beta \)-arrestin recruitment.\(^18\) In mice and rats, TRV130 is potently analgesic while causing less gastrointestinal dysfunction and respiratory suppression than morphine at equianalgesic doses.\(^18\) These results suggest a promising preclinical profile for TRV130.\(^18\)

In early clinical studies in healthy volunteers, TRV130 has demonstrated both dose-linear pharmacokinetics (increases in geometric mean maximum plasma concentration and area under the concentration-time curve extrapolated to infinity 12% greater than dose-proportional) and exposure-related pharmacodynamics (dose-related, marked pupil constriction correlated with TRV130 plasma concentration, suggesting a strong relationship between TRV130 dose, plasma concentrations, and central nervous system pharmacology).\(^34\) TRV130 at various doses administered to healthy volunteers demonstrated an equianalgesic or greater analgesic effect than morphine 10 mg during the cold pressor test, a well-characterized experimental pain...
while demonstrating less impact on hypercapnic respiratory drive and less severe nausea than morphine at these equianalgesic or greater analgesic doses.\textsuperscript{33} Together with the evolving mechanistic understanding of \(\mu\)-opioid receptor \(\beta\)-arrestin function, the preclinical and experimental clinical profile of TRV130 suggests that G protein bias may improve \(\mu\)-opioid receptor function to deliver increased efficacy, improved tolerability, or both. However, this concept has not been previously tested in patients with acute pain.

Here, we present the results of an adaptive-design, phase 2 study investigating TRV130 in patients experiencing moderate-to-severe acute pain after bunionectomy surgery.

2. Methods

2.1. Study design and oversight

This was a randomized, double-blind, adaptive-design study in patients experiencing postoperative pain after bunionectomy (NCT02100748). The primary objective of this study was to demonstrate proof-of-concept for analgesic efficacy of TRV130 vs placebo. The secondary objectives were to evaluate analgesic efficacy vs morphine, evaluate the tolerability of TRV130 in patients with acute postoperative pain after bunionectomy, and perform dose-strength ranging and dose-interval ranging for TRV130. The study was conducted at 4 U.S. research centers between April and October 2014. Study procedures were approved by an institutional review board and complied with the International Conference on Harmonisation Guidance for Industry and the Declaration of Helsinki.\textsuperscript{19} All participants provided written informed consent. Trevena, Inc (the study sponsor); Cytel, Inc; and Premier Research designed the study. Cytel, Inc, performed statistical analyses using a prespecified analysis plan.

2.2. Patients

Men and women aged 18 to 75 years with weight \(\geq 45\) kg and body mass index (BMI) \(\leq 40\) kg/m\(^2\) were enrolled. We excluded patients with severe systemic disease,\textsuperscript{2} history of clinically significant conditions contraindicative of study medication, potentially confounding comorbidities such as comorbid painful conditions or hepatic or renal conditions that could affect study medication metabolism, recent frequent analgesic use, opioid tolerance or physical dependence, substance abuse, or postbunionectomy complications. Patients underwent primary, unilateral, first metatarsal bunionectomy with osteotomy and internal fixation under regional anesthesia using a ropivacaine 0.5% popliteal sciatic nerve block and optional Mayo block. Regional anesthetic infusion was continued postoperatively with mepivacaine 0.5% until approximately 3 AM on postoperative day 1. During this period, supplementary analgesia was first permitted using popliteal sciatic nerve block manipulation, then second-line hydrocodone/acetaminophen 7.5/325 mg every 4 hours (q4h) as needed (pm), then third-line intravenous (IV) or intramuscular ketorolac 30 mg (or 15 mg) q6h pm.\textsuperscript{1} Patients were eligible to receive study medication if they reported a numeric rating scale (NRS)\textsuperscript{7} pain intensity \(\geq 4\) within 9 hours after discontinuation of regional anesthesia.

2.3. Study procedures

The 2-phase, adaptive design methodology is detailed elsewhere.\textsuperscript{10} In summary, the pilot phase randomized 144 patients in a 1:1:1:1:1:1 ratio to 48-hour treatment with TRV130 at 1, 2, 3, or 4 mg IV q4h; placebo IV q4h; or morphine 4 mg IV q4h to initially test estimated dose regimens and efficacy measurement time points to determine dose regimens used in the second phase.

The pilot phase regimens were then analyzed by an Adaptation and Data Review Committee (ADRC) using a construct of CU, defined as levels of efficacy (time-weighted average [TWA] change in NRS pain intensity over 48 hours [NRS TWA0-48] for TRV130 minus that for morphine) vs levels of intolerability (prevalence of vomiting for TRV130 minus that for morphine), and the initial TRV130 regimens for the second phase were selected.\textsuperscript{19}

The second phase randomized successive 25-patient cohorts to 2 adaptively chosen TRV130 dose regimens, placebo or morphine 4 mg (q4h) in an 8:8:4:5 ratio, with analysis of CU between each cohort to select TRV130 doses for successive cohorts. The dose interval for TRV130 was changed from 4 hours to 3 hours, and the range of dose strengths was lowered after analysis of CU in the pilot phase. In the second phase, TRV130 doses of 0.5, 1, 2, and 3 mg q3h were evaluated. The sample size for the study was originally planned to combine the pilot phase and the second phase and have 90% power (\(\alpha = 0.05, 1\)-sided, SD = 2) to identify a 1-unit difference on the NRS between TRV130 (N \(\geq 80\) at dose with maximum CU) and placebo (N = 65).\textsuperscript{19}
The randomization schedules for the pilot phase and second phase were prepared by Cytel, Inc, before the beginning of each phase. Medication was prepared at the study site by unblinded site pharmacists and administered by blinded site personnel. Only unblinded personnel were able to access the database containing dose assignments. Unblinded personnel did not conduct any efficacy or tolerability assessments. Blinded personnel administered study medication in double-blind fashion in the pilot phase; double-dummy binding was used in the second phase to mask the different dose intervals for TRV130 (c3h) and morphine (q4h).

2.4. Rescue medication

Patients were encouraged to wait 1 hour after the first dose of study medication before receiving rescue medication, consisting of first-line acetaminophen 650 mg q4h pm, then second-line intramuscular or IV ketorolac 30 mg (or 15 mg) q6h pm.† Patients whose pain was not adequately controlled with study and rescue medication were discontinued from the study. All patient rescue medication use was captured.

2.5. Measures

As described above, the pilot phase initially tested efficacy measurement time points (baseline; 5, 10, 15, 30, and 45 minutes; and 1, 1.5, 2, 3, 4, 5, 6, 8, 9, 12, 16, 18, 20, 24, 28, 30, 32, 36, 40, 42, 44, and 48 hours). For the second phase of the study, NRS pain intensity and categorical pain relief were assessed at baseline and at specified time points over 48 hours: 5, 10, 15, 30, and 45 minutes; 1, 1.5, 2, 3 hours (prior to dose administered at hour 3); 3.25, 4.25, 5.25, 6.25, 7.25, 8.25, 9.25, 10.25, 11.25, 12.25, 13.25, 14.25, 15.25, 16.25, 17.25, 18.25, 21.25, 24 hours (prior to the dose administered at hour 24); 24.25, 27.25, 30.25, 33.25, 36.25, 39.25, 42.25, 45.25, and 48 hours; as well as before rescue medication and before study discontinuation. Time to onset of analgesia was determined using the 2-stopwatch method, for which patients were given 2 stopwatches and instructed to stop the first for perceptible improvement and the second for meaningful improvement. Categorical pain relief was assessed at specified time points listed above using a 5-point scale (“none,” “a little,” “some,” “a lot,” and “complete”). Patients were asked open-ended questions regarding adverse events (AEs); vital sign measurements, physical examinations, clinical laboratory testing, and electrocardiography were performed at scheduled times. Oxygen saturation was measured using a finger tip pulse oximeter, which was monitored continuously and recorded at 30 and 45 minutes and at 1, 1.5, 2, 3, 4, 5, 6, 8, 9, 12, 16, and 24.5 hours. If an asymptomatic decrease in oxygen saturation >5% compared with baseline occurred for >1 minute, it was remeasured within 2 minutes. If confirmed, study medication was discontinued.

2.6. End points

The primary end point was the NRS TWA0-48, calculated as the area under the 0- to 48-hour pain intensity curve (AUC) divided by 48 hours, minus the baseline pain intensity. Secondary efficacy end points included NRS TWA in the first 3 hours (NRS TWA0-3); stopwatch time to perceptible pain relief; meaningful pain relief; and the onset of analgesia, defined as the time to perceptible pain relief in patients who went on to experience meaningful pain relief; proportion of patients using rescue pain medication; categorical distribution of pain relief; and time to peak categorical pain relief. Safety and tolerability were evaluated by the incidence of AEs and physical examination, while vital signs, clinical laboratory testing, and electrocardiography assessments were compared with baseline values. Oxygen saturation measurements at predefined time points to 24.5 hours were compared with baseline values.

2.7. Statistical analyses

The efficacy analysis population consisted of all patients who received any study medication and had ≥1 postbaseline NRS score. The tolerability analysis population consisted of all patients who received any study medication. The primary efficacy analysis was performed using an analysis of covariance model including treatment effect as the independent factor and baseline pain intensity, gender, and study site as covariates via sequential analysis of each dose, beginning with the highest, compared with placebo using 1-sided, step-down trend testing with a significance level of 0.05. This is a sequential testing approach in which the Type I error rate of $\alpha = 0.05$ is maintained for testing each dose vs placebo for the primary end point, and failure of any dose in the sequence (beginning with the highest dose and stepping down to each next-lower dose in sequence) implies automatic failure of all subsequent lower doses. Missing NRS scores were imputed using baseline observation carried forward imputation after withdrawals due to lack of efficacy or AEs, and last observation carried forward imputation after withdrawals due to other reasons. TWA calculations of NRS in the second phase included both scheduled and unscheduled pain assessments, such as those performed immediately before rescue medication use, and the actual time of each assessment was used in the calculation. No imputation was performed after rescue medication use. Other NRS TWA analyses were performed similarly. Stopwatch times used the Kaplan-Meier method and log-rank P values. Categorical pain relief comparisons used the Cochran-Mantel-Haenszel test. Comparison of proportion of patients receiving rescue medication was performed using Fisher’s exact test. Safety and tolerability end points used descriptive statistics; oxygen saturation change from baseline integrated over time was calculated as the trapezoidal AUC for the change from baseline oxygen saturation over time. Analysis of CU between cohorts to select TRV130 doses for successive cohorts incorporated NRS TWA0-48 and the prevalence of vomiting events for TRV130, both compared with morphine.

3. Results

3.1. Disposition of patients

Enrollment of 400 patients was planned, but the study ended after treatment of 333 patients after the ADRC determined that the study objectives were met. In the pilot phase, 141 of 144 patients randomized were treated with TRV130 1, 2, 3, or 4 mg q4h; placebo; or morphine 4 mg q4h. Of those, 134 of 141 patients (95.0%) completed the study, and withdrawal rates were generally similar across treatment groups. Ten patients were discontinued early from the study in the pilot phase: 2 withdrew because of AEs, 2 withdrew consent, 4 were discontinued because of investigator decision, and 2 were discontinued for other reasons. In the second phase, a total of 195 patients were randomized, and 192 patients were treated with TRV130 0.5, 1, 2, or 3 mg q3h; placebo; or morphine 4 mg q4h, representing the full analysis set. Sixteen patients were discontinued early from the
study in the second phase: 5 because of AEs, 2 after withdrawal of consent, 4 because of investigator decision, 4 because of lack of efficacy, and 1 for another reason.

### 3.2. Demographics and baseline characteristics

Demographics were similar for both phases of the study: The population was predominantly female (128/141, 90.8% in the pilot phase; 169/192, 88.0% in the second phase), white (120/141, 85.1% in the pilot phase; 141/192, 73.4% in the second phase), and middle aged (mean standard deviation [SD] age: 42.8 [12.36] years in the pilot phase; 40.0 [11.81] years in the second phase). Although the onset and magnitude of TRV130 efficacy was demonstrated in the pilot phase, TRV130 analgesic efficacy was not maintained for the entire 4-hour dosing interval and q4h dosing was deemed suboptimal by the ADRC; thus, TRV130 dosing shifted to q3h for the second phase and, therefore, the second phase data are reported hereafter. Morphine was administered q4h for the duration of the study to be consistent with typical dosing and administration instructions. In the second phase, demographic and baseline characteristics of treated patients were generally similar among treatment groups except for a higher number of males in the morphine group (20.5%) than in the other groups (6.5%-11.1%; Table 1). Patients were aged 18 to 67 years, with a mean (SD) of 40.0 (11.81) years, and were predominantly female (88.0%) and white (73.4%). Mean (SD) weight was 72.6 (13.00) kg and BMI was 26.7 (4.15) kg/m². Mean (SD) baseline NRS pain intensity was 6.9 (1.82), consistent with previous bunionectomy studies[14,15,38] and similar between treatment groups.

During the pilot phase, TRV130 1, 2, 3, or 4 mg q4h were used to determine optimal dosing regimens for the second phase. This close-range testing for CU revealed that, while TRV130 produced significant analgesia during the first 12 hours at 3 mg and 4 mg q4h, the q4h dosing period resulted in loss of analgesia between doses, preventing TRV130 from meeting the primary end point over 48 hours during the pilot phase. As the pilot phase was designed as a dose-finding phase and the protocol permitted the dosing interval to be adjusted up to q6h or down to q3h, the dosing interval was reduced to q3h for the second phase of the study.

#### 3.3. Efficacy

##### 3.3.1. Primary end point

TRV130 2 and 3 mg met the primary end point, producing statistically greater least-squares (LS) mean (95% confidence interval) reductions in NRS TWA0-48 than placebo, as did morphine (TRV130 q3h: 0.5 mg, −0.5 [−1.6 to 0.6], P = 0.1832; 1 mg, −0.3 [−1.3 to 0.6], P = 0.2311; 2 mg, −1.4 [−2.3 to −0.4], P = 0.0024; 3 mg, −2.4 [−3.3 to −1.4], P < 0.0001; morphine 4 mg, −1.3 [−2.3 to −0.4], P = 0.0023). In a prespecified secondary analysis, the NRS TWA0-48 for TRV130 3 mg was significantly improved compared with morphine 4 mg (P = 0.0144). The effect of gender was considered in a sensitivity analysis using the primary efficacy model. No significant gender effect and no significant gender-by-treatment interaction were found (P > 0.2 for each).

##### 3.3.2. Secondary end points

Secondary end points reflecting the magnitude of efficacy demonstrated that TRV130 produced up to a 6-point group mean (SD) decrease in NRS pain intensity at 10 minutes after

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### Table 1

<table>
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<tr>
<th>Demographic and baseline characteristics for second phase.</th>
<th>Placebo (N = 28)</th>
<th>TRV130 0.5 mg q3h (N = 29)</th>
<th>TRV130 1 mg q3h (N = 36)</th>
<th>TRV130 2 mg q3h (N = 36)</th>
<th>TRV130 3 mg q3h (N = 31)</th>
<th>Morphine 4 mg q4h (N = 38)</th>
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<td>Mean ± SD</td>
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Data presented as n (%) unless otherwise noted. BMI, body mass index; q3h, every 3 hours; q4h, every 4 hours; SD, standard deviation.
administration (−6.0 [1.91]; Fig. 2). In the first 3 hours, both TRV130 2 mg and 3 mg produced statistically lower pain intensity than morphine 4 mg, with NRS TWA0-3 of −1.2 (P = 0.0029) and −1.8 (P < 0.0001), respectively, vs morphine. The proportion of patients achieving meaningful pain relief increased with TRV130 dose up to 96.8% with TRV130 3 mg (56.4% with morphine; 35.7% with placebo) (Fig. 3A). Increasing TRV130 doses produced greater peak categorical pain relief after the first dose; by the 3-mg dose, all patients reported pain relief as either “complete” or “a lot” (Fig. 3B) with shifts to these categories for TRV130 compared with both placebo (TRV130 0.5, 1, 2, and 3 mg: 5/20 [25%], P = 0.0461; 21/38 [55.3%], P < 0.0001; 30/36 [83.3%], P < 0.0001; placebo: 0/28 [0%]) and morphine (16/39 [41.0%], P = 0.0005 and P < 0.0001 vs TRV130 2 and 3 mg, respectively).

Considering other secondary end points of efficacy, TRV130 produced a dose-related decrease in median stopwatch time to the onset of analgesia in the first 30 minutes (placebo: 30 minutes; TRV130 0.5, 1, 2, and 3 mg: 3.0, 3.5, 2, and 1 minutes, respectively); and for morphine, 6 minutes. Median stopwatch time to meaningful pain relief for TRV130 was also dose related and, at doses of ≥1 mg, more rapid than placebo, as was morphine (TRV130 1 mg, P = 0.0165; 2 mg, P = 0.0007; 3 mg, P < 0.0001; morphine, P = 0.0089; Fig. 3C). The median time to achieve peak categorical pain relief also shortened with increasing TRV130 dose and occurred earlier in the 48-hour treatment period; by contrast, peak categorical pain relief with placebo and morphine occurred later in treatment (TRV130 2 mg, P = 0.0042; 3 mg, P = 0.0025; morphine, P = 0.0374; Fig. 3D).

As is typical for the bunionectomy model,5,15,22 the majority of patients received rescue medication at least once during the treatment period. All patients treated with placebo (28/28) received rescue medication at some point during the treatment period. Among placebo-treated patients, the median (95% CI) time to first use of rescue medication was 1.3 [1.1-2.2] hours, whereas patients receiving TRV130 2 mg or 3 mg q3h, or morphine q4h first received rescue pain medication at 3.2 [1.7-11.5] hours, 5.0 [1.9-12.6] hours, and 5.3 [1.6-18.9] hours, respectively. Among patients receiving TRV130, the proportion of patients receiving rescue medication decreased as dose increased (18/20 [90.0%], 33/38 [86.8%], 29/36 [80.6%], and 22/31 [71.0%] for TRV130 0.5, 1, 2, and 3 mg, respectively); for morphine, 29 of 39 patients (74.4%) received rescue medication. Significantly fewer patients administered TRV130 2 mg (P = 0.0153) or 3 mg q3h (P = 0.0022) or morphine 4 mg q4h (P = 0.0037) and received rescue medication compared with those who received placebo.

3.4. Safety and tolerability

Adverse events reported with TRV130 were typical ORAEs.6 No serious AEs (SAEs) were reported in either phase of the study. The most frequent AEs reported in patients in all active treatment groups were nausea, dizziness, headache, and vomiting, and for TRV130, were generally dose related, as was the severity of AEs (Table 2). Analyses of vital signs, physical examination, clinical laboratory testing, and electrocardiography assessments revealed only modest, generally dose-related μ-opioid effects, such as decreased blood pressure and heart rate. Five TRV130 patients receiving 1, 2, or 3 mg q3h discontinued because of AEs: 4 with hypotension (investigator-graded mild to moderate) and 1 with tachycardia (graded mild). As the intolerability parameter for CU analyses between cohorts, the prevalence of TRV130 vomiting events was dose related and greatest with TRV130 3 mg.

Although the absolute changes were small and not deemed clinically significant, the integrated mean (SD) percent change from baseline in oxygen saturation over 0 to 24.5 hours was numerically smaller for TRV130 than for morphine (placebo, −2.1 [29.66]%·hour; TRV130 0.5, 1, 2, and 3 mg, −1.5 [33.53]%·hour, 0.5 [28.70]%·hour, 2.3 [24.66]%·hour and −5.1 [32.37]%·hour; morphine, −14.5 [28.77]%·hour).

![Figure 2. Numeric rating scale pain intensity over 48 hours in patients after bunionectomy. SE, standard error.](image)
4. Discussion

Recent preclinical work has suggested that engaging a subset of μ-opioid receptor signaling may enhance the therapeutic index of opioids by increasing the window between doses that produce efficacy and those that produce certain AEs.9,30 Additionally, ORAEs are a significant clinical concern in patients with acute pain.11 Ultimately, the unmet medical need in acute pain therapy is an increased level of efficacy with acceptable tolerability.24 This study investigated the structurally and pharmacologically novel μ-opioid receptor biased ligand TRV130 in patients experiencing moderate-to-severe acute pain after bunionectomy, a validated model for the evaluation of acute analgesics.14,15,38 Between the pilot and second phase, 8 unique TRV130 dose-regimens were evaluated, allowing broader dose-strength (6-fold) and dose-interval (q3h and q4h) ranging than typically executed with a parallel design.32,37 In the second phase, TRV130 at doses of 2 and 3 mg q3h significantly reduced pain intensity over 48 hours compared with placebo, achieving the primary end point of the study. TRV130 3 mg also produced a statistically and clinically significant 1-point difference in NRS TWA0-48 compared with morphine 4 mg. Secondary findings were supportive, with generally dose-related effects on measures of analgesic magnitude and rate of effect.

As is typical for the bunionectomy model, the dynamic range of NRS pain intensity scores became more limited in the later hours of the study, as postoperative pain resolved and rescue medication was administered.14–16,38 Although the primary end point measured the 48-hour treatment period, the earlier portion of the study had larger dynamic range with greater levels of pain intensity. Therefore, assessing efficacy in this time window allowed for a clearer understanding of magnitude of effect, dose-response, and duration of action.

The completion rate in this study was 93%, higher than is typical for the bunionectomy model, for which there are several possible explanations. First, the majority of patients in all treatment groups but placebo reported pain relief. Second, adequate rescue medication was available throughout the randomized treatment period. Third, randomized treatment began on postoperative day 1 with adequate analgesia provided until that time, decreasing the likelihood that a patient would enter the randomized treatment period with unmanageable pain. Finally, the investigators and sites involved in the study were experienced with the bunionectomy model, trained for consistency in study management before the trial onset, and staffed with personnel who were experienced in both the model and analgesic methodology.

TRV130 3 mg produced a 6-point group mean decrease in NRS pain intensity at 10 minutes after treatment, a magnitude of efficacy that has not previously been demonstrated in acute pain studies, based on our review of the literature. Subsequent TRV130 doses reduced pain to a similar level. The majority of patients who received TRV130 1 mg or more reported meaningful pain relief, with nearly all patients reporting meaningful pain relief with TRV130 3 mg. Although it may be possible to achieve this analgesic efficacy with conventional opioids, potential...
intolerability and the specter of respiratory depression often precludes more effective dosing. In this study, TRV130 produced this efficacy in the absence of SAEs, suggesting that greater analgesia can be achieved safely.

The time to peak categorical pain relief occurred progressively earlier as TRV130 dose increased, and at the TRV130 higher doses, occurred considerably earlier (<5 minutes) than with morphine (>20 minutes). Patients receiving TRV130 reported a dose-related improvement in categorical pain relief after the first dose, with doses of 2 and 3 mg TRV130 performing better than morphine 4 mg. This rapidity of onset and predictability of analgesic efficacy of TRV130 warrant further study, as these performance characteristics could facilitate titration to pain relief while avoiding ORAEs.

TRV130 produced dose-related ORAEs—most commonly, nausea, dizziness, headache, and vomiting. Two factors may have influenced the pattern of AEs in this trial. First, the fixed, forced-dosing regimen did not permit dose reduction according to patient factors, baseline pain intensity, or on-treatment pain intensity, and reductions may have mitigated AEs. In early clinical development, the fixed administration paradigm allows for a more thorough understanding of the potential therapeutic profile of TRV130, including dose-response, duration of effect, safety, and tolerability. TRV130 administered in a more clinically relevant fashion, via patient-controlled analgesia, is being studied in a soft-tissue pain model (NCT02335294).

In summary, this study demonstrated TRV130 analgesic efficacy for the treatment of moderate-to-severe acute pain was achieved without SAEs. Although proof of concept was demonstrated for analgesic efficacy, robust tolerability comparisons were limited by dosing methodology and modest sample size, and future studies are needed to continue to assess tolerability. These results also suggest CU for TRV130 at different points on the dose-response curve: Higher doses may provide previously unachieved reductions in pain intensity in clinical scenarios that require greater analgesia, with dose reduction as an option to preserve sufficient analgesia with fewer ORAEs than experienced with conventional opioids.

The analgesic efficacy of TRV130 for the treatment of moderate-to-severe acute pain was achieved without SAEs. Although proof of concept was demonstrated for analgesic efficacy, robust tolerability comparisons were limited by dosing methodology and modest sample size, and future studies are needed to continue to assess tolerability. These results also suggest CU for TRV130 at different points on the dose-response curve: Higher doses may provide previously unachieved reductions in pain intensity in clinical scenarios that require greater analgesia, with dose reduction as an option to preserve sufficient analgesia with fewer ORAEs than experienced with conventional opioids.

In summary, this study demonstrated TRV130 analgesic efficacy in patients experiencing moderate-to-severe acute pain in a bunionectomy model. In-study comparisons to morphine suggest that G-protein-biased μ-opioid receptor activation may enable increased efficacy with acceptable tolerability vs conventional opioids.

Conflict of interest statement
Supported by Trevena, Inc. E. R. Viscusi has received consulting fees from Mallinckrodt Pharmaceuticals, Cubist Pharmaceuticals, Salix Pharmaceuticals, Inc, and Trevena, Inc; and has received grants and consulting fees from AcelRx Pharmaceuticals, Inc, and Pacira Pharmaceuticals, Inc, outside the submitted work. L. Webster has received consulting fees from BioDelivery Sciences International, Inc, Grunenthal USA, Inc, Mallinckrodt Pharmaceuticals, Depomed, Inc, Egalet Corp, Inspiron Pharmaceuticals, INSYS Therapeutics, Inc, Orexo AB (publ), Pfizer, Inc, Teva Pharmaceutical Industries Ltd, and Trevena, Inc, during the conduct of the study; and has received consulting fees from AstraZeneca plc, Bristol-Myers Squibb Company, Cara Therapeutics, CVS/Caremark, Jazz Pharmaceuticals plc, Kaleo, Inc, Nektar Therapeutics, Nevro Corp, and has received grants and consulting fees from AcelRx Pharmaceuticals, Salix Pharmaceuticals, Inc, and Trevena, Inc; and has received grants and consulting fees from AcelRx Pharmaceuticals, Salix Pharmaceuticals, Inc, and Trevena, Inc; and has received grants and consulting fees from AcelRx Pharmaceuticals, Salix Pharmaceuticals, Inc, and Trevena, Inc.
Proove Biosciences, Signature Therapeutics, Inc, and Synchrony Healthcare Group, LLC; outside the submitted work. J. A. Bolognese and S. Zuckerman are employees of Cytel, Inc, contracted by the sponsor to assist with study design and statistical analysis. S. Daniels and M. Kuss are employees of Premier Research, contracted to manage the study on behalf of Trevena, Inc. D. G. Soergel, R. A. Subach, E. Cook, and F. Skobieranda are employees of the study’s sponsor, Trevena, Inc.

The adaptive design of this study, without presentation of study results, has been presented in detail in the following manuscript: Bolognese JA, Subach RA, Skobieranda F. Evaluation of an adaptive maximizing design study based on clinical utility versus morphine for TRV130 proof-of-concept and dose-regimen finding in patients with postoperative pain after bunionectomy. Ther Innovation & Regul Sci 2015; 49:756–66.

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References
[33] Soergel RG, Subach RA, Burnham N, Lark MW, James IE, Sadler BM, Skobieranda F, Violin JD, Webster LR. Blinded agonism of the mu-opioid receptor by TRV130 increases analgesia and reduces on-target adverse effects versus morphine: a randomized, double-blind,


