An orally available μ-opioid receptor biased ligand is analgesic with reduced constipation in rodents

Jonathan D. Violin, PhD, Scott M. DeWire, PhD, Mike Koblish, Daniel Chen, PhD, Aimee L. Crombie, PhD, Dennis Yamashita, PhD, Ruth Ann Subach, PharmD, David G. Soergel, MD, and Michael W. Lark, PhD
Trevena Inc, King of Prussia, PA

Introduction

• Morphine elicits both analgesia and treatment-limiting adverse effects, including constipation and respiratory depression, through the μ-opioid receptor.
• Morphine exerts increased analgesia but decreased constipation and respiratory depression in β-arrestin2 knockout mice (1, 2).
• “Biased ligands” selectively engage subsets of receptor signals and unlock the potential for novel, improved GPCR-targeted therapeutics (3).

Approach

• Trevena’s small molecule library was screened for novel opioid receptor ligands
• Hits were optimized for potency, efficacy, bias, selectivity, and pharmacokinetics.
• Pharmacology tested in a battery of standard rodent models of opioid action.

Results

• TRV130 and TRV734 are potent opioids with reduced β-arrestin recruitment vs. morphine

Hypothesis: a G protein-biased μ-opioid receptor ligand will avoid β-arrestin-mediated constipation and respiratory depression to deliver safer, better tolerated analgesia than morphine

• TRV130 and TRV734 have high oral PK in non-human primates

• TRV130 and TRV734 robustly engage G protein coupling with efficacy and potency comparable to morphine, but display dramatically reduced β-arrestin coupling.
• In rodents, TRV130 and TRV734 are potently analgesic, but display reduced gastrointestinal dysfunction compared to morphine.
• The improved therapeutic index of TRV130 and TRV734 could allow safer, more effective pain management by removing key barriers to effective opioid therapy.
• TRV130 also has reduced impact on respiratory suppression compared to morphine, and is in development for treating post-operative pain.
• TRV734 is in preclinical development for the treatment of acute and chronic pain.
• 25 ng/mL TRV130 in plasma at ED50 for morphine response in healthy volunteers suggests efficacious oral exposure of TRV130 of 100-350 mg/s based on extrapolation of in vitro and rodent potencies.

Conclusions

• TRV130 and TRV734 are novel, potent, and selective G protein biased μ-opioid receptor ligands.
• TRV130 and TRV734 robustly engage G protein coupling with efficacy and potency comparable to morphine, but display dramatically reduced β-arrestin coupling.
• In rodents, TRV130 and TRV734 are potently analgesic, but display reduced gastrointestinal dysfunction compared to morphine.
• The improved therapeutic index of TRV130 and TRV734 could allow safer, more effective pain management by removing key barriers to effective opioid therapy.
• TRV130 also has reduced impact on respiratory suppression compared to morphine, and is in development for treating post-operative pain.
• TRV734 is in preclinical development for the treatment of acute and chronic pain.
• 25 ng/mL TRV130 in plasma at ED50 for morphine response in healthy volunteers suggests efficacious oral exposure of TRV130 of 100-350 mg/s based on extrapolation of in vitro and rodent potencies.

References

Figure 1. Pharmacology of TRV130 in vitro. A: Equianalgesic dosages of morphine, oxycodone, and TRV130 in the hot plate assay. B: Time (hours) to maximum effect (% max morphine response) vs. Concentration (-log M) for morphine, oxycodone, and TRV130. C: Equianalgesic dosages of morphine, oxycodone, and TRV130 in the morphine challenge assay. D: Time (hours) to maximum effect (% max morphine response) vs. Concentration (-log M) for morphine, oxycodone, and TRV130.

Figure 2. Mice were administered morphine, TRV130, or TRV734 by subcutaneous bolus, followed by testing 30 minutes later. Maximum, possible effect = 20-second latency in 50° hot plate, 240-minute retention in glass bead assay, and zero fecal bolus production, all compared to values in vehicle-treated animals.

Figure 3. Pharmacological effects of TRV130 and TRV734. A: Comparison of μ-opioid receptor agonist activity of TRV130 and TRV734 in the ED50 for morphine response in healthy volunteers and the maximal possible effect in mice. B: Time (hours) to maximum effect (% max morphine response) vs. Concentration (-log M) for morphine, oxycodone, and TRV130 in the hot plate assay. C: Comparison of μ-opioid receptor agonist activity of TRV130 and TRV734 in the ED50 for morphine response in healthy volunteers and the maximal possible effect in mice. D: Time (hours) to maximum effect (% max morphine response) vs. Concentration (-log M) for morphine, oxycodone, and TRV130 in the morphine challenge assay. E: Comparison of μ-opioid receptor agonist activity of TRV130 and TRV734 in the ED50 for morphine response in healthy volunteers and the maximal possible effect in mice. F: Time (hours) to maximum effect (% max morphine response) vs. Concentration (-log M) for morphine, oxycodone, and TRV130 in the hot plate assay.

Figure 4. Mice were administered oxycodone or TRV130 by oral gavage, followed by testing 30 minutes later. Maximum, possible effect = 20-second latency in 50° hot plate or 240-minute retention in glass bead assay, all compared to values in vehicle-treated animals.

Figure 5. Healthy volunteers (56 per drug group) were infused with TRV130 or 1 hour. Doses 14 mg were well-tolerated, with nausea and vomiting dose-limiting at 7 mg. A: TRV130 Cmax and AUC were dose linear; half-life was approximately 2 hours. B: Pupil size change at 70 minutes in relationship to TRV130 exposure at 60 minutes shows a dose-response relationship consistent with established opioid pharmacology. Data are mean ± s.e.m. in ClinicalTrials.gov identifier: NCT00157178.

Figure 6. Healthy volunteers (56 per drug group) were infused with TRV130 for 1 hour. Doses 14 mg were well-tolerated, with nausea and vomiting dose-limiting at 7 mg. A: TRV130 Cmax and AUC were dose linear; half-life was approximately 2 hours. B: Pupil size change at 70 minutes in relationship to TRV130 exposure at 60 minutes shows a dose-response relationship consistent with established opioid pharmacology. Data are mean ± s.e.m. in ClinicalTrials.gov identifier: NCT00157178.

Figure 7. TRV734 causes less constipation than oxycodone.

TRV130 and TRV734 cause less constipation than morphine in mice

• TRV130 and TRV734 cause less constipation than morphine in mice

TRV130 PK/PD in healthy volunteers

• TRV130 and oral TRV34 may have greater tolerability than is achievable with current opioids