# Formulation and Food Effect Studies of TRV734, an Oral, G Protein-biased Ligand of the μ-opioid Receptor

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Biased ligands. Better drugs.

## Purpose

- Conventional opioids such as morphine are effective and potent analgesics to treat moderate-to-severe acute pain; however, typical adverse effects (AEs) such as constipation, nausea, vomiting, sedation and respiratory depression can be intolerable and possibly life-threatening
- The pharmacological actions of conventional opioids are mediated primarily through the μ-opioid receptor, a G protein-coupled receptor
- Prior research has shown that biased ligands that selectively activate G protein coupling of the μ-opioid receptor without significantly stimulating β-arrestin recruitment potentiate analgesic activity with reduced constipation and respiratory depression
- We present here the results from 3 open-label crossover studies of TRV734, an investigational oral, G protein-biased ligand of the μ-opioid receptor, examining the pharmacokinetics (PK) of various formulations and the effect of food on bioavailability in healthy adult male subjects

## Methods

**Study 1**
- Open-label, randomized sequence, 3-period crossover study in 12 healthy male subjects
- Each subject received the following treatments:
  - TRV734 125 mg as a capsule in the fasted state
  - TRV734 125 mg as an oral solution in the fasted state
  - TRV734 125 mg as a capsule following a standard meal

**Study 2**
- Open-label, randomized sequence, 3-period crossover study in 13 healthy male subjects
- Each subject received the following treatments:
  - TRV734 125 mg administered following a high-fat meal
  - TRV734 125 mg administered following a standard meal
  - TRV734 125 mg administered in 3 split portions over 120 minutes in the fasted state

**Study 3**
- Open-label, 4-period crossover study in 18 healthy male subjects
- Immediate-, slow-, medium-, and slow-release formulations chosen based on relative dissolution rates
- Each subject received 4 of the following 6 treatments in the fasted state on Days 1, 3, 5 and 7:
  - A: TRV734 150 mg immediate-release capsule
  - B: TRV734 50 mg medium-release tablet
  - C: TRV734 150 mg medium-release tablet
  - D: TRV734 150 mg slow-release tablet
  - E: TRV734 50 mg immediate-release capsule + TRV734 150 mg medium-release tablet
  - F: TRV734 50 mg immediate-release capsule + TRV734 150 mg slow-release tablet

## Results

### Study 1

**Food did not affect bioavailability of TRV734**

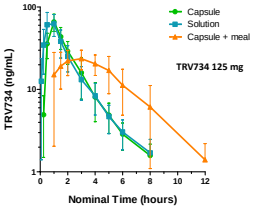


**Figure 1. Mean (± 95%CI) TRV734 plasma concentrations over time after dosing as a single oral capsule or oral solution in the fasted state, and as a capsule after a high-fat meal.** There was no significant difference in TRV734 bioavailability given as a solution or drug in capsule to fasted subjects. When drug in capsule was given to subjects following a high fat meal, absorption was slowed, resulting in decreased peak concentrations, but total exposure (AUC) was not affected.

**Adverse events**

| | Capsule Fasted N=11 | Solution Fasted N=11 | Capsule Fed N=12 | Total N=12 |
|---|---|---|---|---|
| **Any TEAE** | **7 (63.6) [10]** | **10 (90.9) [14]** | **4 (33.3) [6]** | **11 (91.7) [30]** |
| Somnolence | 3 (27.3) [3] | 3 (27.3) [3] | 1 (8.3 [1] | 5 (41.7) [7] |
| Feeling hot | 2 (18.2) [2] | 1 (9.1) [1] | 2 (16.7) [2] | 3 (25.0) [5] |
| Feeling of relaxation | 2 (18.2) [2] | 2 (18.2) [2] | 1 (8.3 [1] | 3 (25.0) [5] |
| Dizziness | 2 (18.2) [2] | 2 (18.2) [2] | 1 (8.3 [1] | 2 (16.7) [5] |
| Dysgeusia | 0 | 1 (9.1) [1] | 0 | 1 (8.3) [1] |
| Headache | 1 (9.1) [1] | 0 | 0 | 1 (8.3) [1] |
| Cold sweat | 0 | 1 (9.1) [1] | 0 | 1 (8.3) [1] |
| Pruritis | 0 | 1 (9.1) [1] | 0 | 1 (8.3) [1] |
| Nausea | 0 | 0 | 1 (8.3 [1] | 1 (8.3) [1] |
| Contusion | 0 | 1 (9.1) [1] | 0 | 1 (8.3) [1] |
| Euphoric mood | 0 | 1 (9.1) [1] | 0 | 1 (8.3) [1] |
| Dyspnoea | 0 | 1 (9.1) [1] | 0 | 1 (8.3) [1] |

number of patients (% of patients) [# of events]

### Study 2

**Food or split dosing did not affect bioavailability of TRV734**

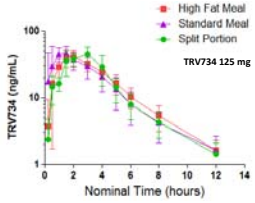


**Figure 2. Mean (± 95%CI) TRV734 plasma concentrations over time after dosing as a single oral capsule to subjects in different feeding states.** There was no appreciable difference in TRV734 peak or total exposure when dosed following a standard or high fat meal, or as 3 split portions over 120 minutes in the fasted state. Time to peak ($t_{max}$) was longer for TRV734 when dosed as split portions

**Adverse events**

| | High fat n=12 | Standard fat n=13 | Split portion n=12 | Total n=13 |
|---|---|---|---|---|
| **Any TEAE** | **5 (41.7) [6]** | **6 (46.2) [13]** | **4 (33.3) [9]** | **10 (76.9) [28]** |
| Nausea | 0 | 2 (15.4) [2] | 2 (16.7) [2] | 4 (30.8) [4] |
| Somnolence | 0 | 3 (23.1) [3] | 1(8.3) [1] | 3 (23.1) [4] |
| Dizziness | 2 (16.7) [2] | 0 | 0 | 2 (15.4) [2] |
| Constipation | 0 | 1 (7.7) [1] | 1 (8.3) [1] | 2 (15.4) [2] |
| Vomiting | 0 | 2 (15.4) [2] | 0 | 2 (15.4) [2] |
| Feeling of relaxation | 2 (16.7) [2] | 0 | 0 | 2 (15.4) [2] |
| Abdominal pain | 0 | 0 | 1 (8.3) [1] | 1 (7.7) [1] |
| Flatulence | 1 (8.3) [1] | 0 | 0 | 1 (7.7) [1] |
| Application site irritation | 0 | 0 | 1 (8.3) [1] | 1 (7.7) [1] |
| Chest discomfort | 0 | 0 | 1 (8.3) [1] | 1 (7.7) [1] |
| Feeling drunk | 1 (8.3) [1] | 0 | 0 | 1 (7.7) [1] |
| Headache | 0 | 0 | 1 (8.3) [1] | 1 (7.7) [1] |
| Paraesthesia | 0 | 1 (7.7) [1] | 1 (8.3) [1] | 1 (7.7) [2] |
| Blood calcium increased | 0 | 1 (7.7) [1] | 0 | 1 (7.7) [1] |
| Oxygen saturation decreased | 0 | 1 (7.7) [1] | 0 | 1 (7.7) [1] |
| Vertigo | 0 | 1 (7.7) [1] | 0 | 1 (7.7) [1] |
| Hyperhidrosis | 0 | 1 (7.7) [1] | 0 | 1 (7.7) [1] |

number of patients (% of patients) [# of events]

### Study 3

**TRV734 showed prolonged exposure when given as modified-release formulations**

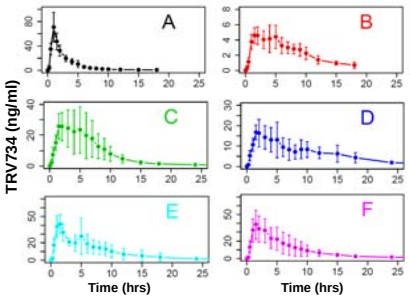


**Figure 3. Mean TRV734 (± 95%CI) concentrations over time after dosing.**
A: TRV734 150 mg immediate-release capsule
B: TRV734 50 mg medium-release tablet
C: TRV734 150 mg medium-release tablet
D: TRV734 150 mg slow-release tablet
E: TRV734 50 mg immediate-release capsule + TRV734 150 mg medium-release tablet
F: TRV734 50 mg immediate-release capsule + TRV734 150 mg slow-release tablet
All modified-release formulations (B-F) show prolonged absorption and a lower $C_{max}$ relative to the immediate-release capsule (A).

**Adverse events**

| | A N=12 | B N=12 | C N=12 | D N=12 | E N=12 | F N=12 | Total N=18 |
|---|---|---|---|---|---|---|---|
| **Any TEAE** | **1 (8.3 [1]** | **1 (8.3 [1]** | **2 (16.7) [2]** | **1 (8.3 [1]** | **2 (16.7) [5]** | **1 (8.3 [1]** | **8 (44.4) [11]** |
| Dizziness | 0 | 0 | 1 (8.3) [1] | 1 (8.3) [1] | 0 | 1 (8.3) [1] | 3 (16.7) [3] |
| Headache | 1 (8.3) [1] | 0 | 0 | 0 | 1 (8.3) [1] | 0 | 2 (11.1) [2] |
| Constipation | 0 | 1 (8.3) [1] | 1 (8.3) [1] | 0 | 0 | 0 | 2 (11.1) [2] |
| Nausea | **0** | 0 | **0** | 0 | 2 (16.7) [3] | 0 | 2 (11.1) [3] |
| Vomiting | **0** | 0 | **0** | 0 | 1 (8.3) [1] | 0 | 1 (5.6) [1] |

number of patients (% of patients) [# of events]

**Study 1**
- Eleven of 12 subjects received all three TRV734 treatments
- The $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ for the fasted state were generally similar for capsule vs. solution, indicating similar pharmacokinetics for these formulations
- The $C_{max}$ was 47% lower for the fed than for the fasted state (geometric LS means ratio [90% CI]: 0.53 [0.46, 0.61]); however, the geometric LS means ratios for AUCs were close to 1 for the fed vs fasted states, with the 90% CIs within the range of 0.8 to 1.25
- All treatments were well-tolerated, with no serious AEs or AEs leading to early discontinuation

**Study 2**
- Twelve of 13 subjects received all three TRV734 treatments
- The geometric LS means ratios of high-fat/standard-fat, standard-fat/split-portion fasted state, and high-fat/split-portion fasted state for $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ were close to 1, indicating similar bioavailability of TRV734 for the 3 treatments
- The median $t_{max}$ occurred later when TRV734 125 mg was administered as 3 split portions over 120 minutes under fasted conditions (~3 hours) compared to administration under fed conditions without splitting the dose (~1.5 hours)
- All treatments were well-tolerated, with no serious AEs or AEs leading to early discontinuation

**Study 3**
- All 18 subjects completed the study, with each subject receiving 4 of the 6 formulations
- As expected, Treatment A had a higher $C_{max}$ (50% - 70%) than the other formulations
- In terms of overall exposure based on AUC, Treatments C, D, E, and F were all similar to Treatment A; the $t_{max}$ for Treatments E and F (1.0 - 1.5 hours) were similar to Treatment A (1.0 hour)
- In comparison with each other, Treatments C, E, and F showed similar bioavailability in terms of $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$, higher bioavailability compared to Treatment D, based on dose-normalized comparisons, and much higher bioavailability compared to Treatment B
- The $t_{max}$ for Treatments E and F (1.0 - 1.5 hours) was similar to Treatment D (1.75 hours), with median $t_{max}$ for Treatments B (2.0 hours) and C (3.0 hours) occurring slightly later
- There was a longer apparent t½ for Treatments D and F (5.4 - 5.7 hours) vs. other treatments (2.0 - 3.6 hours)
- All treatments were well-tolerated, with no serious AEs or AEs leading to early discontinuation

## Conclusions

- Various fast-dissolution-rate capsule and modified-release formulations of TRV734 have similar bioavailability, suggesting that TRV734 is absorbed throughout the gastrointestinal tract
- Food did not significantly alter TRV734 exposure
- In Study 3, treatments C, D, E and F (medium- and slow-release tablets 150 mg in the absence [C, D] or presence [E, F] of immediate-release capsule 50 mg) show potential as modified-release formulations, demonstrating prolonged exposure relative to the immediate-release capsule; dosing these modified-release formulations every 6 to 8 hours may be feasible
- In these studies, TRV734 was well-tolerated, with no serious AEs or AEs leading to early discontinuation