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

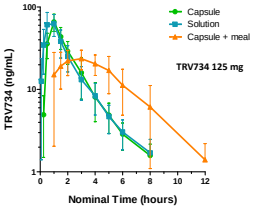

Figure 1. Mean (± 95%CI) TRV734 plasma concentrations over time after dosing as a single oral capsule or oral solution in the fasted state, and as a capsule after a high-fat meal. There was no significant difference in TRV734 bioavailability given as a solution or drug in capsule to fasted subjects. 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

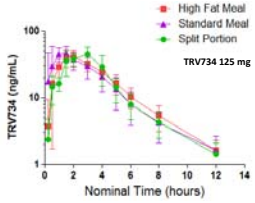

Figure 2. Mean (± 95%CI) TRV734 plasma concentrations over time after dosing as a single oral capsule to subjects in different feeding states. There was no appreciable difference in TRV734 peak or total exposure when dosed following a standard or high fat meal, or as 3 split portions over 120 minutes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

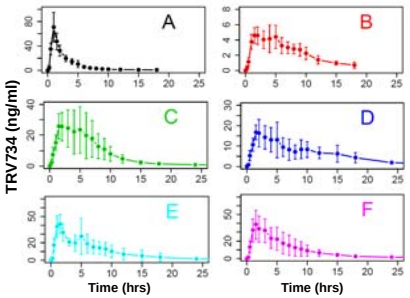

Figure 3. Mean TRV734 (± 95%CI) concentrations over time after dosing.
A: TRV734 150 mg immediate-release capsule
B: TRV734 50 mg medium-release tablet
C: TRV734 150 mg medium-release tablet
D: TRV734 150 mg slow-release tablet
E: TRV734 50 mg immediate-release capsule + TRV734 150 mg medium-release 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