W142

A Phase 1 Healthy Volunteer Study of the Safety, Tolerability and Pharmacokinetics of TRV250, a G Protein-Selective Delta Receptor Agonist

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BACKGROUND

- Migraine headache (MH) is defined as a neurologic disease characterized by severe headache pain, associated with or without aura (defined as a temporary neurologic disturbance of the sensory or motor functions (1)
- It is often associated with visual disturbances, nausea, vomiting, dizziness and photophobia (1)
- Both vascular and neuronal components are involved in the pathophysiology, with local vasodilation and simultaneous release of sensory neuropeptides, including calcitonin gene-related peptide (CGRP), Substance P (SP), serotonin, contributing to neurogenic inflammation contributing to the pain in MH (2)
- Delta-opioid receptors (DORs) are known to be involved in the presynaptic inhibition of SP and CGRP release (3)
- Diffuse dural innervation peptidergic CGRP-expressing C fibers co-express the DOR, suggesting that agonists of the DOR could exert anti-migraine effects in part by inhibition of CGRP release (4), providing a novel therapy for the treatment of MH
- The available evidence suggests that DOR agonists have a low potential for abuse
- TRV250 is a novel small molecule agonist of the DOR that acts in a manner preferentially selective for G protein signaling, with relatively little activation of the β-arrestin2 post-receptor signaling pathway
- β-arrestin2 recruitment is linked to DOR-mediated convulsions, and reduced recruitment of β-arrestin is associated with lack of seizure activity (5)
- TRV250 significantly reduces nitroglycerin-evoked hyperalgesia in rodents, a model used to screen candidates for potential utility in acute migraine
- We report on the first-in-human (FIH) study of TRV250 in healthy volunteers given single subcutaneous (SC) and oral doses of TRV250

OBJECTIVES

- To evaluate the safety and tolerability of single ascending doses of TRV250 relative to placebo when given by SC injection to healthy adult males or females
- To evaluate the single-dose PK of TRV250 when given by SC injection to healthy adult males or females
- To evaluate the safety and tolerability of TRV250 when given as a single oral dose as a capsule in the fed or fasted state to healthy adult males or females.
- To evaluate the PK and bioavailability of TRV250 when given as a single oral dose capsule in the fed or fasted state, relative to a SC injection, in healthy adult males or females

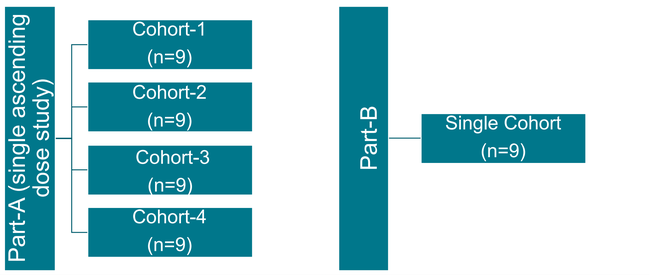
METHOD

Study Design

Two part, randomized, single-blind, placebo-controlled study of TRV250 in healthy volunteers

2 active SC doses and 1 placebo dose; separated by 5 days (dose range: 0.1 – 30 mg) All injections in the abdomen

TRV250 administered as a single 6 mg oral dose in either the fasted or fed state



Inclusion criteria
- Healthy male or female subjects 18-50 years old
- Body weight > 50 kg, BMI 18-32 kg/m^2
- Capable of giving informed consent
- Healthy, as defined by history, physical exam, vital signs, ECG, EEG and lab tests

Female subjects were required to use a highly effective contraceptive method

Male subjects were required to use barrier methods of birth control for 90 days after the last dosing period

Exclusion criteria
- Significant CNS, cardiac, pulmonary, metabolic, renal or GI conditions
- Abnormal ECG, QTcF> 450 msec, abnormal EEG at screening
- AST/ALT> ULN at screening, positive urine test for drugs of abuse, positive HIV, HepB or HepC tests
- History of smoking
- Previous participation in a clinical trial within 30 days or 5 half-lives of the previous medication
- The use of any prescription or non-prescription medications
- Consumption of grapefruit or grapefruit juice within 14 days prior to dosing
- Currently breast-feeding, or planning to start breast-feeding within 90 days of final dose

ECG Evaluation

- Any subject who met the following criteria were withdrawn from the study:
  - QTcF> 500 msec or uncorrected QT> 600 msec
- Change from baseline QTcF> 60 msec at any time-point during the study
- If the above was observed in 2 or more subjects at a given dose level, dosing at that level would cease, and no further dose escalation would occur

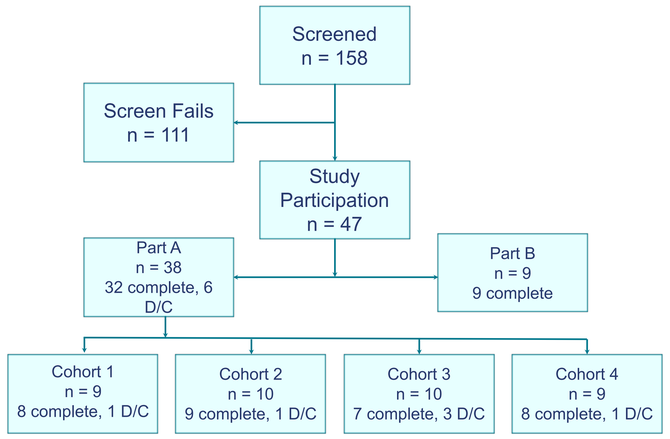
EEG Evaluation

- EEGs performed at screening to exclude subjects with spike/sharp wave abnormalities with eyes open/closed, during hyperventilation and photic stimulation
- During the study, spontaneous EEGs were collected over 10 minute intervals pre-dose, and at 0.25, 0.5, 1 and 4 hours post-dose
- EEGs evaluated by two blinded central EEG raters prior to each dose escalation

RESULTS

Subject Disposition (Figure 1)

Figure 1: Subject Accountability



Demographics (Table 1)

Table 1: Demographics –Parts A and B

Characteristic	Part A (n = 38)	Part B (n = 9)
Caucasian n (%)	36 (94.7)	9 (100)
Females n(%)	17 (44.7)	4 (44.4)
Age (years) Mean (SD) [min, max]	31.8 (9.7) [18, 48]	26.0 (8.57) [18, 43]
BMI (kg/m^2) Mean (SD) [min, max]	25.2 (3.19) [19.6, 31.3]	24.1 (2.91) [19.7, 28.2]

Part A Pharmacokinetics Results (Table 2, Figure 2A)

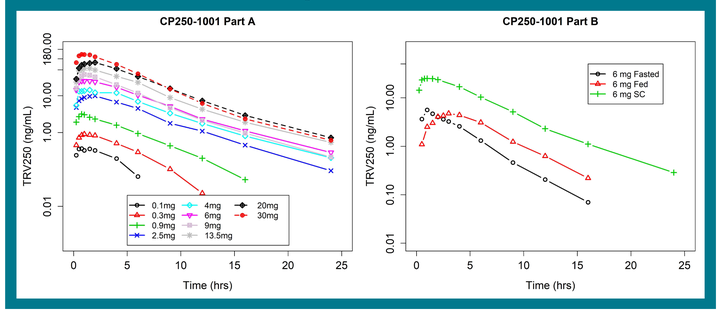
- Absorption of TRV250 after SC injection was rapid, with average peak concentrations reached at about 0.5-2.0 hours post-dose
- Both AUC and Cmax increased in a linear manner with dose
- Mean half-life ranged between 2.39-3.76 hours
- After the peak, plasma concentrations decreased in a monophasic manner

Table 2: Summary of TRV250 Pharmacokinetics (Part A)

Dose	Cmax[a] (ng/mL)	Tmax[b] (hr)	AUCinf[a] (ng*h/mL)	t½[a] (hr)
0.1 mg (N=6)	0.388 (34.0%) [0.240-0.568]	1 [0.5-1.5]	2.81(15.9%) [2.27-3.46]	2.80 (34.7%) [2.06-5.14]
0.3 mg (N=5)	0.950 (13.6%) [0.774-1.10]	1 [0.5-1.5]	5.47 (11.3%) [5.04-5.69]	2.39 (17.9%) [1.94-3.00]
0.9 mg (N=6)	3.18 (33.7%) [2.27-5.15]	0.75 [0.5-1.03]	15.7 (14.6%) [13.2-19.3]	2.64 (27.7%) [1.82-3.52]
2.5 mg (N=7)	10.5 (11.7%) [9.26-12.5]	1.5 [0.5-2]	60.8 (30.7%) [43.6-96.8]	2.72 (26.1%) [1.93-3.97]
4.0 mg (N=6)	16.8 (36.6%) [11.0-25.8]	1.53 [0.5-4.35]	97.7 (23.1%) [77.9-141]	3.49 (15.8%) [3.05-4.61]
6.0 mg (N=6)	30.2 (26.5%) [20.4-42.2]	1.13 [0.5-2.07]	157 (21.8%) [120-217]	3.64 (28.4%) [2.33-5.00]
9.0 mg (N=6)	38.7 (32.0%) [27.8-60.2]	1.26 [0.75-1.5]	187 (18.0%) [160-244]	3.37 (27.7%) [2.13-4.37]
13.5 mg (N=6)	56.5 (20.2%) [38.7-69.1]	1.25 [0.75-2]	318 (19.0%) [256-412]	3.76 (21.6%) [2.58-4.63]
20 mg (N=5)	79.6 (24.7%) [58.2-102]	2 [1-2]	474 (27.5%) [377-698]	3.39 (21.8%) [2.78-4.87]
30 mg[c] (N=16)	151 (20.9%) [97.8-230]	1 [0.5-2]	652 (17.9%) [522-939]	3.17 (21.6%) [2.29-4.53]

a geometric mean (geometric CV%) [min-max]
b Median [min-max]
c data from DP1-3 combined, n=1

Figure 2: (A): Part A Mean TRV250 plasma concentrations vs. time by dose. (B): Part B Mean TRV250 plasma concentrations vs. time by treatment



Part B Results (Table 3, Figure 2B)

- Peak concentrations of TRV250 occurred later after oral administration (1-3 hours) as compared with SC administration (0.5-2.0 hours), and were further delayed when administered with a high fat meal (3-6 hours)
- Concentrations achieved after an oral dose (both fed and fasted) were significantly lower than those observed following an SC dose

Table 3: Summary of TRV250 Pharmacokinetics (Part B)

Treatment	Cmax[a] (ng/mL)	Tmax[b] (hr)	AUC(0-∞)[a] (ng*hr/mL)	t½[a] (hr)
Fed (6 mg)	5.28 (40.1%) [2.61-7.68]	3.22 [3-6]	31.6 (34.2%) [17.0-50.3]	2.60 (21.6%) [1.69-3.32]
Fasted (6 mg)	6.06 (24.3%) [4.82-8.59]	1 [1-3]	22.8 (25.3%) [16.2-30.8]	2.52 (31.1%) [1.60-4.12]

a: geometric mean (geometric CV) [min-max]
b: median [min-max]

Relative Bioavailability

- Oral bioavailability was lower as compared to SC administration, in both the fasted and fed states
- Relative bioavailability in the fed state (19.1%) is higher than that in the fasted state (13.8%)

Safety

- In Part A, 29/38 subjects experienced at least 1 treatment-emergent adverse event (TEAE)
  - All were mild except for 4 moderate AEs (3 subjects)
    - Pain at injection site (placebo)
    - Headache (0.9 mg TRV250)
    - Postural orthostatic tachycardia (0.1 mg TRV250)
  - Most common AEs: injection site pain, headaches
  - No clinically relevant changes in ECGs, EEGs, suicidal ideation, hematology, chemistry
- In subjects receiving TRV250 in Part B, 4 subjects experienced at least 1 TEAE in the fasted state, and 2 in the fed state

CONCLUSION

- TRV250 was well tolerated, with the most common AEs of pain at injection site and headaches, both of which were mild in most subjects and were not dose-related
- There were no serious TEAEs reported and no TEAEs leading to death. One subject receiving TRV250 0.1 mg discontinued due to a TEAE
- There were no clinically relevant changes in physical exams, ECGs, EEGs, suicidal ideation, hematology, clinical chemistries, or urinalysis observed after TRV250 administration
- There were no clinically relevant changes in vital signs with the exception that there were some TRV250-related orthostatic changes (symptomatic or asymptomatic) in some subjects
- There were no clinically significant changes from baseline observed upon review of EEGs in individual subjects
- Peak and total exposures increase proportionally with dosing between 0.1 mg to 30 mg SC
- Half-life was consistent across all doses, ranging between 2.39 and 3.76 hours
- The oral bioavailability of TRV250 was 14% to 20% relative to SC
- TRV250 administered with food reduced the rate of absorption, with a later T_{max}, a higher AUC_{inf} (138%), and a slightly lower C_{max} (87%), when compared to administration in the fasted state

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Disclosure
TRV 250 is an investigational drug developed by Trevena, Inc. Funding for this study was provided by Trevena, Inc. Layout of the poster was done by Lark & Co.Creative, funding for which was provided by Trevena, Inc.

Presented at the 58th Annual meeting of The American College of Neuropsychopharmacology (ACNP), December 8-11, 2019; Orlando, FL