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 peptide 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 (5)
• TRV250 significantly reduces nitroglycerin-evoked hyperalgesia in rodents, a model used to screen candidates for potential utility in acute migraine (6)
• 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

- Cohort 1: 32 complete
- Cohort 2: 10 complete
- Cohort 3: 10 complete
- Cohort 4: 9 complete

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
• There were no clinically relevant changes in physical exams, ECGs, EEGs, or lab tests

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

RESULTS

Table 1: Demographics – Parts A and B

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Part A (n=38)</th>
<th>Part B (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian (%)</td>
<td>30 (79%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Females (%)</td>
<td>17 (44%)</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53 (17-56)</td>
<td>51 (30-67)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>21 (8.8)</td>
<td>21 (6.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.3 (6.3)</td>
<td>24.9 (4.4)</td>
</tr>
</tbody>
</table>

Table 2: Summary of TRV250 Pharmacokinetics (Part A)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Cmax a (ng/mL)</th>
<th>Tmax b (hr)</th>
<th>AUCCmaxc (ng·h/mL)</th>
<th>t1/2 d (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 mg</td>
<td>0.388 (34.9%)</td>
<td>0.5 (5.5)</td>
<td>2.81 (19.9%)</td>
<td>2.8 (34.7%)</td>
</tr>
<tr>
<td>0.3 mg</td>
<td>0.950 (13.6%)</td>
<td>1 (1.5)</td>
<td>4.47 (11.3%)</td>
<td>2.39 (17.9%)</td>
</tr>
<tr>
<td>0.6 mg</td>
<td>1.463 (21.2%)</td>
<td>1.5 (2.0)</td>
<td>6.04 (15.6%)</td>
<td>2.84 (27.1%)</td>
</tr>
<tr>
<td>2.5 mg</td>
<td>10.5 (11.7%)</td>
<td>1.5 (3.0)</td>
<td>60.3 (30.7%)</td>
<td>2.72 (26.1%)</td>
</tr>
<tr>
<td>4.0 mg</td>
<td>16.3 (38.6%)</td>
<td>1.5 (3.5)</td>
<td>89.7 (23.1%)</td>
<td>3.14 (18.5%)</td>
</tr>
<tr>
<td>6.0 mg</td>
<td>30.3 (32.5%)</td>
<td>2.0 (4.0)</td>
<td>137 (21.8%)</td>
<td>3.74 (28.4%)</td>
</tr>
<tr>
<td>8.0 mg</td>
<td>38.7 (32.0%)</td>
<td>2.5 (5.0)</td>
<td>187 (19.0%)</td>
<td>3.37 (27.7%)</td>
</tr>
<tr>
<td>13.5 mg</td>
<td>56.5 (20.2%)</td>
<td>3.0 (6.0)</td>
<td>318 (19.0%)</td>
<td>3.76 (21.6%)</td>
</tr>
<tr>
<td>20 mg</td>
<td>78.6 (24.3%)</td>
<td>3.5 (7.0)</td>
<td>474 (27.9%)</td>
<td>3.39 (21.8%)</td>
</tr>
<tr>
<td>30 mg</td>
<td>151 (20.9%)</td>
<td>4.0 (8.0)</td>
<td>652 (17.9%)</td>
<td>3.17 (21.6%)</td>
</tr>
</tbody>
</table>

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

d: geometric mean (geometric CV%) [min-max]

Figure 1: Subject Accountability

Table 3: Summary of TRV250 Pharmacokinetics (Part B)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cmax a (ng/mL)</th>
<th>Tmax b (hr)</th>
<th>AUCCmaxc (ng·h/mL)</th>
<th>t1/2 d (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fed (6 mg)</td>
<td>6.28 (40.1%)</td>
<td>3.72</td>
<td>31.5 (34.2%)</td>
<td>2.01 (21.6%)</td>
</tr>
<tr>
<td>Fasted (6 mg)</td>
<td>6.06 (24.3%)</td>
<td>1 (1-3)</td>
<td>22.8 (25.3%)</td>
<td>2.52 (31.1%)</td>
</tr>
</tbody>
</table>

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, hematologic, 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 Tmax, a higher AUCCmax (138%), and a slightly lower Cmax (87%), when compared to administration in the fasted state

REFERENCES

2. Melchior F. Ann Indian Acad Neurol. 2016;19(175-82)

DISCLOSURE

TRV 250 is an investigational drug developed by Trevena, Inc. Funding for this study was provided by Trevena, Inc.