SENSITIVITY OF PUPILLOMETRY IN TRACKING PHARMACODYNAMIC EFFECTS OF A NOVEL OPIOID, TRV130, IN A FIRST IN MAN TRIAL IN HEALTHY SUBJECTS

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Background

- μ-opioid agonists are powerful but problematic analgesics in post-operative pain. Respiratory depression, nausea and vomiting, constipation and sedation can be dose-limiting and prevent effective pain control[1,2,3]
- TRV130 is a novel, selective, G protein-biased ligand at the μ-opioid receptor, stimulating G protein coupling with potency and efficacy similar to morphine[4]
- In preclinical studies TRV130 was potently analgesic while causing less respiratory depression and gastrointestinal dysfunction than morphine, suggesting unique benefits in acute pain management[4]
- As part of the first human studies with TRV130, pupillometry was included as a non-invasive technique to attempt to demonstrate target engagement.
- Opiates have been shown to cause dose-related decreases in pupil size and in the velocity of reaction to a light stimulus via central activation of the μ-opioid receptor[5]

Aims

- To use pupillometry assessments to demonstrate that TRV130 could cross the blood-brain barrier and engage with the μ-opioid receptor
- To utilize evidence of appropriate target engagement to help guide the selection of the starting dose for future patient/efficacy trials

Methods

Study Design

- Randomized, single-blind, placebo-controlled, parallel group, single-ascending dose study in healthy male subjects
- TRV130/placebo administered as a 1-hour constant dose continuous infusion
- Each dose level contained 8 subjects (2 received placebo and 6 TRV130)
- 8 dose levels of TRV130 were investigated; 0.15, 0.25, 0.4, 0.7, 1.2, 2.2, 4 and 7mg
- The TRV130 starting dose was selected based on the preclinical toxicology studies with subsequent doses determined by tolerability

Subject Disposition

Table (1) Subject Age by Treatment Group

	0.15	0.25	0.4	0.7	1.2	2.2	4	7	Pl
Mean Age	**29.5**	**26.3**	**31.3**	**38.5**	**33.7**	**32.3**	**28.5**	**30.5**	**28.3**
SD	**8.76**	**5.65**	**9.37**	**9.65**	**11.54**	**9.00**	**8.38**	**11.69**	**7.88**
Sample Size	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**16**

- Subjects were healthy males who met all inclusion/exclusion criteria and had a BMI between 18.0 and 32.0 kg/m^2

Pupillometry Assessments

- Pupillometry recorded by a Neuroptics PLR-200 pupillometer
- Subjects were dark adapted using red-light goggles for 3 minutes prior to measurements
- Pupil diameter was measured at baseline and 10, 30, 60, 120 and 180 minutes after completion of drug infusion

Results

TRV130

- TRV130 was safe and well tolerated
- Nausea and vomiting occurred only in the 7mg dose, all other dose levels experienced low numbers of adverse events
- TRV130 demonstrated dose-proportionality across the range of doses investigated
- TRV130 concentration at the end of the 1-hour infusion was dose-linear

Pupillometry

Table (2) Pupil Diameter x Time

	0.15 mg	0.25 mg	0.4 mg	0.7 mg	1.2 mg	2.2 mg	4 mg	7 mg	Placebo
Sample Size	6	5	6	6	6	6	6	6	16
Predose	6.232	6.210	6.442	5.595	6.386	5.855	6.728	6.270	6.970
70 min	6.093	5.976	6.078	5.295	6.034	4.577	4.078	2.897	6.849
90 min	6.083	6.258	6.285	5.018	6.172	4.848	4.060	3.145	6.691
120 min	5.935	6.343	6.212	5.607	6.286	5.135	4.455	3.317	6.783
180 min	6.413	6.220	6.360	5.697	6.280	5.538	5.487	5.123	6.561

- Small decreases in pupil diameter (miosis) noted at 0.4mg dose
- TRV130 elicited marked miosis at doses of 2.2mg and above, which lasted for at least three hours post infusion
- Peak miosis occurred 10 minutes after the end of the infusion and was dose-related
- TRV130 did not produce AEs that prevented full data recording at any dose level investigated

Discussion

- This study successfully demonstrated that TRV130 was able to cross the blood-brain barrier and interact with the μ-opioid receptor in a dose-dependent manner, consistent with that seen with other opioid analgesics
- TRV130, at doses ranging from 1.2-4mg, elicited pupil constriction of 0.4-2.7mm, which in other studies has correlated with an analgesic effect of therapeutic doses of IV morphine (2-8mg) and buccal fentanyl (100-400μg)[5]

Conclusions

- Inclusion of pupillometry assessments into a first in human trial provided rapid evidence of appropriate target engagement and enabled an appropriate starting dose of TRV130 to be identified for use in subsequent patient trials
- These data support further evaluation of TRV130 to determine whether G protein bias at the μ-opioid receptor offers advantages in pain management compared to classic unbiased opioid ligands

References

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