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(376) TD-1211 demonstrates tolerability and clinical activity following multiple treatment administration strategies in patients with opioid-induced constipation (OIC)

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The primary objective of this Phase 2, single-blind study was to assess safety and tolerability of various doses, dosing strategies and dose escalations of TD-1211, an orally administered and peripherally selective mu opioid antagonist. Secondary objectives assessed efficacy of TD-1211. Ninety-five chronic non-cancer pain OIC patients were enrolled into six cohorts. The first four cohorts received 5mg once daily for either four or two days, respectively, followed by an increase in daily dose to either 10mg or 15mg for two weeks. Cohort five received 2mg once daily and cohort six received 2.5mg q6h, respectively, for two weeks without dose escalations. TD-1211 was generally well tolerated. For the combined data, irrespective of dose, the most common TEAEs (occurring $\geq$ 5%) were abdominal pain (14.7%), nausea (9.5%), flatulence (8.4%), diarrhea (6.3%), headache (6.3%), and abdominal distension (5.3%). During the 4-day and 2-day initiation periods, respectively, 9.4% and 18.8% of subjects reported GI-related AEs. All AEs were transient and resolved without sequelae. Across cohorts, the mean baseline spontaneous bowel movements (SBMs) and complete SBMs (CSBMs) ranged from 0.9 to 1.7 and 0.1 to 0.6, respectively. During Week 2, the 10mg and 15mg dose cohorts showed a mean change from baseline in SBM and CSBM frequency ranging from 3.3 to 5.4 SBMs/week and 2.8 to 4.4 CSBMs/week. The 2mg TD-1211 dose demonstrated minimal activity, with a mean increase from baseline during Week 2 of 1.8 SBMs and 0.7 CSBMs. The 2.5mg q6h regimen was clinically active, with a mean increase from baseline at Week 2 of 4.3 SBMs and 4.5 CSBMs. There were no reports of central opioid withdrawal during the study and no clinically relevant changes in ECGs, laboratory exams, or vital signs. These results support further development of a 5mg treatment initiation dose followed by maintenance therapy at up to 15mg QD.

(377) Bridging from conventional marketed immediate release formulations to new tamper resistant alternatives

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Many solid immediate release (IR) dosage forms containing opioids can be abused by snorting of crushed product or preparation of solutions for subsequent injection. Tamper resistant IR formulations (TRF-IR) aim to prevent intentional abuse by crushing and dissolving. Gruenenthal (GRT) has developed a TRF technology (INTAC®) for extended release formulations, already available as marketed products. The technology has now been expanded for IR formulations using also a high molecular weight polymer as excipient. A switch from a conventional immediate release formulation to TRF product alternatives generally requires bridging bioequivalence studies. A GRT-TRF IR formulation (Test) was investigated in an open, randomized, cross-over, relative bioavailability trial against the reference marketed IR formulation of an analgesic product. Single oral doses were administered to healthy male subjects under fasted conditions. Serum drug concentrations were determined by a validated LC-MS/MS method. Non-compartmental PK analysis was performed and the usual 80.00-125.00% confidence interval acceptance criteria for bioequivalence were used for comparing Test to the reference. The 90% confidence intervals for Cmax and AUC0-t of Test were 89.74 - 117.32% and 94.24-109.97%, respectively. The data demonstrate that GRT-TRF-IR tablets have comparable in-vivo performance to standard immediate release formulations. TRF-IR tablets may enable physicians to simply switch patients from conventional to reformulated TRF products. The study was sponsored by Gruenenthal GmbH.

(378) Ketamine IV in outpatient setting: effective treatment for neuropathic pain syndromes

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Ketamine is an antagonist of NMDA-type glutamate receptors, These play a strong promoting role in pain transmission in the CNS, in sub-anesthetic doses. We have also used this for migraines and headaches. This is an ongoing study of this agent for treating pain flareups in neuropathic pain syndromes. 389 patients (264=f, 125=m) were treated for pain flareups. All had allodynia or hyperalgesia in the region of pain, Conditions treated were: CRPS (n=126), cervical/lumbar radiculopathy (n=145), TN (n=34), TMD (n=47), pelvic/vulvodynia pain (n=37). 285 patients had co-existent headache/migraine. Antecubital IV was placed; pulse oximetry monitoring was used in each patient. Patients rated their pain on a 0-10 VAS both before treatment and at 15 minute intervals during and after treatment. 0.25-0.30 mg ketamine/kg was administered by IV infusion over 120-180 minutes. Another 0.30 mg/kg, or slightly higher dose ,was administered again over the same time. Up to 4 infusions were given, not necessarily on the same day. We defined success as greater than 50% reduction in pain VAS from baseline. Beginning pain (8.45/10) reduced to 2.03/10 after treatment ($p < .001$, 2 tailed t test). Average ketamine infusion time was 149 min; average ketamine dose was 185.6mg. Time of pain reduction was 4.4 days (range = 26 hrs to 233 hrs). Side effects were transient spaciness/calm (n=344). Allodynia was gone in all but 2 patients. 12 patients reported less than 25% reduction in pain. 271 patients reported better than 50% decrease in headache. Our data supports NMDA-type glutamate receptor over-activity in many neuropathic pain disorders, with great efficacy, safety and tolerability for the treatment.

(379) An orally available mu-opioid receptor biased ligand is analgesic with reduced constipation in rodents

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Morphine elicits increased analgesia and decreased constipation and respiratory depression in beta-arrestin2 knockout mice compared to wild-type mice. These effects are all mediated by the mu-opioid receptor, which couples to both G proteins and beta-arrestins, suggesting that drugs selectively engaging G protein coupling may offer increased opioid analgesia with improved safety and tolerability. Trevena has previously described TRV130, a G protein-biased mu-opioid receptor ligand in clinical testing for post-operative analgesia. In preclinical testing, TRV130 showed reduced gastrointestinal dysfunction and respiratory depression compared to equianalgesic doses of morphine. We have subsequently identified TRV734, a molecule with in vitro and in vivo pharmacology highly similar to TRV130. TRV734 robustly engages G protein coupling with efficacy comparable to morphine, oxycodone, and oxymorphone, but displays dramatically reduced beta-arrestin coupling. By both subcutaneous and oral routes, TRV734 is strongly analgesic in rodents, but displays marked improvement in constipation and respiratory depression when compared to subcutaneous morphine or oral oxycodone. Preclinical pharmacokinetics suggest that TRV734 may have good oral availability in humans. The improved therapeutic index of TRV734 could allow safer, more effective pain management than currently used opioids. Supported by Trevena Inc., King of Prussia, PA.