comparison test criteria, indicating comparable dissolution profiles among aqueous (0% ethanol) and ethanol-containing media. The 100-mg dosage demonstrated a significantly slower dissolution in 40% ethanol and therefore did not pass the f2 test. Ethanol in concentrations of 5%–20% had no clear effect on dissolution rates in either pH 1.2 or pH 6.8. However, a trend showing a decrease in dissolution rates for all dosages was observed with increasing ethanol concentrations, and a significant decrease in dissolution rate was observed with 40% ethanol. No evidence of alcohol dose dumping was observed with morphine ADEI-IMT, and slower dissolution rates occurred at higher alcohol concentrations. Funded by Egale Corporation.

(426) Effect of naldemedine, a peripherally acting \( \mu \)-opioid receptor antagonist, on QT interval

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Naldemedine (NLD) is a peripherally acting \( \mu \)-opioid receptor antagonist being developed for treatment of opioid-induced constipation. According to the International Conference on Harmonization E14 guidelines, to-be-marketed compounds are required to undergo a critical assessment of pro-arrhythmic potential, which can develop from QT (or hear-rate [HR]-corrected QT [QTc]) interval prolongation (regulatory level of concern is > 10 msec). Evaluations should include dosing and both placebo and positive (e.g., pethidine) controls. This study was a double-blind, randomized, placebo- and active-controlled, 4-period cross-over study conducted in healthy adult male and female subjects (n=56). The primary objective was to demonstrate the effect of NLD on QT/QTc intervals. Subjects received a single 0.2 mg dose of NLD, a 1 mg dose of NLD, a 400 mg dose of moxifloxacin or placebo in a cross-over manner. ECG parameters were digitally extracted from a continuous 12-lead ECG recording at baseline and at various post-dose time points. The QTc interval was corrected for HR using Fridericia’s formula (QTcF = QT/RR1/3). Change from baseline in QTcF was calculated at each post-dose extraction time point. After administration of 0.2 and 1 mg doses of NLD, the largest mean placebo-corrected ΔQTcF (ΔΔQTcF) was 1.3 msec (upper bound of the 2-sided 90% confidence interval [CI]: 3.2 msec) at 4 hours post-dose and 0.6 msec (upper bound of the 2-sided 90% CI: 2.5 msec) at 2 hours post-dose, respectively. No subject who received NLD had a QTcF value > 480 msec or a ΔQTcF > 30 msec. The largest mean ΔΔQTcF interval for moxifloxacin was 12.6 msec at 4 hours post-dose with a lower bound of the 2-sided 90% CI > 5 msec. These data demonstrate that NLD is not associated with QTcF prolongation at therapeutic or supra-therapeutic doses. This study was supported by Shionogi Inc.

(427) Novel effects of Euphorbia bicolor (Euphorbiaceae) latex extract on nociceptors

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Opioid-based narcotics are a major component of pain management, but are problematic due to negative side effects mediated by the central nervous system. Pain management can be optimized through discovery of potent non-opioid therapeutics, as well as targeting the peripheral nervous system to avoid side effects. A sub-population of sensory neurons expresses the transient receptor potential V1 ion channel (TRPV1), gated by capsaicin and noxious heat. TRPV1 activation induces release of proinflammatory peptides, including calcitonin gene-related peptide (CGRP), contributing to peripheral sensitization and leading to hyperalgesia. Potent agonists targeting TRPV1, such as capsaicin and resiniferatoxin, produce peripheral analgesia via TRPV1 desensitization and ablation of TRPV1-expressing nociceptors. Resiniferatoxin is extracted from the latex of Euphorbia resinifera. In the same family, Euphorbia bicolor (Euphorbiaceae), native to the Southern United States, displays antioxidant and antiinflammatory properties. E. bicolor latex shares similar phytochemicals, including the irritant Euphorbium, thus may share analgesic properties. We hypothesized that, if the latex of E. bicolor and E. resinifera are similar, then the extract of this color would initially increase CGRP release from sensory neurons followed by a decrease in capsaicin-evoked CGRP release. Rats were decapitated and trigeminal ganglia removed, dissociated, and cultured for 5 days. Cells were then washed and treated with buffer for 15 minutes. Fractures were collected and cells were treated with either vehicle or E. bicolor latex (0, 25, 50, 100, 300 \( \mu \)g/mL) for 15 minutes followed by treatment with vehicle or E. bicolor latex co-treated with capsaicin (50 nM). CGRP was quantified by ELISA. E. bicolor latex treatment induced a twofold increase in CGRP release from trigeminal sensory neurons, similar to the amount of CGRP release stimulated by capsaicin. Capsaicin-stimulated release was reduced following latex treatment compared to vehicle. These data indicate that E. bicolor latex may display similar analgesic properties to TRPV1 agonists.

(428) A randomized, double-blind, parallel Group, placebo-controlled study to evaluate the analgesic efficacy and safety of VVZ-149 injections for post-operative pain following laparoscopic colorectal surgery

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VVZ-149 is a dual antagonist of G\&y2 and SHT2A. G\&y2 blockage increases inhibitory synaptic transmission by glycine in the spinal cord, resulting in a reduction of pain transmissions to the brain.1 SHT2A blockage decreases descending serotonergic facilitatory modulation on pain transmission and reduces nociceptor activation in peripheral nerves.2 VVZ-149 has been shown to have comparable efficacy to morphine in well-controlled animal studies with proven PK/PD correlation. A clinical Phase 1 study performed in healthy subjects has shown no clinically significant adverse events at therapeutic doses.3 We are currently conducting a Phase 2 randomized, double-blind, parallel, placebo-controlled study to evaluate the efficacy and safety of VVZ-149 injections in adults undergoing laparoscopic colorectal surgery. Subjects are being randomized in a 2:1 ratio to two study groups, VVZ-149 injections or placebo initiated in the PACU after surgery. Subjects will receive either VVZ-149 or placebo for 8 hours postoperatively, along with IV hydromorphone as needed by PCA pump. Study participants will be evaluated through 24 hours after dosing with additional follow-up 14-30 days after treatment. The primary outcome, pain relief, will be measured by the sum of pain intensity difference over 8 hours post-dose (SPID-8). Secondary outcomes will include an evaluation of opioid use, pain relief, sedation, nausea, and overall patient satisfaction. Blood samples will be collected at multiple points over 24 hours after dosing to confirm the correlation of PK/PD parameters. (1.Dohi T, et al. Glycine transporter inhibitors as a novel drug discovery strategy for neuropathic pain. Pharmacol Ther. 2009; 5. Okamoto K, et al. 2: Okamoto K, et al. 3-HT2A receptor subtype in the peripheral branch of sensory fibers is involved in the potentiation of inflammatory pain in rats. Pain. 2002; 3.Chung, JY. Phase I Study to Investigate Safety, Tolerability, and Pharmacokinetics of VVZ-149 Injection. In: ClinicalTrials.gov. 2013.) Supported by a grant from Vivozon, Inc.

(429) CREATE-1 study: a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of AXS-02 (disodium zoledronate tetrahydrate) administered orally to subjects with Complex Regional Pain Syndrome Type 1 (CRPS-1)

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The CREATE-1 study is an ongoing Phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of AXS-02 for the treatment of pain associated with CRPS-1. AXS-02 is a potent bisphosphonate compound being developed as an orally administered, non-opioid treatment for pain. The primary endpoint was inhibition of osteoclast activity, and potential effects on pro-inflammatory cytokine production. This Phase IIIa trials plans to enroll 190 subjects who will be randomized 1:1 to receive either placebo or AXS-02 once weekly for 6 weeks. The primary endpoint is the difference from baseline to Week 12, where pain intensity is measured by the weekly average daily pain intensity using the numerical rating scale (NRS). The NRS is an 11-point scale (0-10), reported daily by the subject, where 0 = no pain and 10 = worst pain imaginable. Additional efficacy assessments include: Brief Pain Inventory, pain on motion, signs and symptoms of CRPS, quality of life questionnaires (EQ-SQ and SF-MQ), patient global impression of change, clinician global impression of change, disease recurrence, and markers of bone turnover.
(scTX and P1NP). Assessments of safety include assessment of adverse events, vital signs, and clinical laboratory values. Eligible subjects must be recently diagnosed with CRPS-1 and not currently receiving opioids. The study is composed of 4 phases: Screening phase (up to 3 weeks; assessments for eligibility), Baseline phase (1 week; confirm CRPS-1 score for eligibility), Double-blind Treatment phase (12 weeks; dosing and assessments of efficacy), and Follow-up phase (12 weeks; safety follow-up). An interim analysis will be conducted after 95 patients are enrolled and have completed the double-blind phase of the study.

(430) Bioequivalence and food effect of a novel, abuse-deterrent (AD), extended-release (ER) morphine product candidate compared with a currently available non-AD, ER morphine product. J Dayno, J Lawler, G Niebler, and K Lindhardt; Egalet Corporation, Wayne, PA.

Abuse-deterrent (AD) formulations of opioids have been deemed an important component of risk mitigation for opioid abuse. A novel morphine AD extended-release (ER), injection-molded tablet (ADER-IMT) product candidate has been developed using proprietary Guardian® technology (Egalet Corporation, Wayne, PA) utilizing an injection molding manufacturing process that produces hard tablets that are resistant to rigorous physical and chemical manipulations. The bioequivalence of morphine ADER-IMT and a marketed non-AD morphine ER product were assessed in two phase 1, randomized, open-label, single-dose, crossover studies in healthy adults aged 18–55 years. In study 1 (n=66), fasted subjects received oral morphine ADER-IMT (30 mg), morphine ER (30 mg), or morphine ADER-IMT (2 x 15 mg) in 3 sequential periods. In study 2, one cohort (n=40) received morphine ADER-IMT (60 mg) or morphine ER (60 mg) under fasting conditions in 2 treatment periods; a second cohort (n=25) received morphine ADER-IMT (60 mg) under fed conditions in an additional treatment period. In both studies, all subjects received naltrexone 50 mg before and after each study drug administration. Pharmacokinetic parameters for morphine included area under the plasma concentration vs time curve (AUC) from time 0 to the time of the last quantifiable concentration (AUC0-τ), AUC from time 0 extrapolated to infinity (AUC-inf), and maximum plasma concentration (Cmax). Bioequivalence criteria were from Food and Drug Administration guidelines. In study 1, (fasting conditions) bioequivalence was demonstrated among all 3 treatments (morphine ADER-IMT [30 mg], morphine ER [30 mg], and morphine ADER-IMT [2 x 15 mg]) for all 3 pharmacokinetic parameters. In study 2, bioequivalence was demonstrated between morphine ADER-IMT (60 mg) and morphine ER (60 mg); further, the fed/fast analysis demonstrated no clinically relevant food effect for morphine ADER-IMT (60 mg). Morphine ADER-IMT was generally well tolerated with no unexpected adverse events. Funded by Egalet Corporation.

F15 Opioids in Acute pain

(431) Efficacy of CL-108 compared to hydrocodone 7.5 mg/acetaminophen 325 mg in preventing vomiting and the use of anti-emetics, Opioid-Induced Nausea and Vomiting (OINV). E Hersh, B Schachtel, W Kozaeek, E Schachtel, and M Manino; University of Pennsylvania School of Dental Medicine, Philadelphia, PA.

CL-108 (containing hydrocodone 7.5 mg, acetaminophen 325 mg [HC/APAP] with fast-release promethazine 12.5 mg) was formulated to provide analgesia and prevent opioid-induced nausea and vomiting (OINV). CL-108 has been shown to be an effective analgesic compared to placebo and to significantly reduce the incidence of moderate/severe nausea and vomiting and the use of anti-emetics compared to HC/APAP.1 Another definition of OINV includes two criteria: any vomiting or use of anti-emetics. Because this objective definition is also used to determine the efficacy of a drug in preventing OINV, we used this 2-component endpoint to analyze the results of this study. After surgical extraction of at least 2 impacted molar teeth, 466 patients with moderate-to-severe pain were randomized to self-administer CL-108 (n=211), HC/APAP (n=205), or placebo (n=50) every 4–6 hours as needed for pain. On an hourly basis (while awake) over the first 24 post-op hours patients documented the intensity of pain and nausea and, importantly, the frequency of vomiting and use(s) of an antiemetic. There was 52% less risk of vomiting for patients who used CL-108 compared to HC/APAP-treated patients, who used more doses of anti-emetics than CL-108-treated patients (all p<0.001). HC/APAP-treated patients also used anti-emetics earlier (and more repeated doses) than CL-108-treated patients (p<0.001). Applying the stringent 2-component definition of OINV to these 24-hour results: patients who used CL-108 experienced significantly less OINV than patients who used HC/APAP, representing 64% relative reduction in the risk of developing OINV (p<0.001). We conclude that CL-108 has a substantive effect on the risk of developing OINV, less than a standard treatment for moderate-to-severe pain that contains the same dosages of hydrocodone and acetaminophen. (1. Schachtel B, et al. J Pain. 2014.) Sponsored by Charleston Laboratories and Daiichi Sankyo.


Respiratory safety is an omnipresent clinical concern with conventional parenteral opioids and can even limit dosing required for analgesic efficacy. Conventional opioids bind to μ-opioid receptors and non-selectively activate two downstream signaling pathways: G protein coupling, linked to analgesia, and β-arrestin recruitment, linked to OAREs and limiting efficacy. Oliceridine (TRV130) is a novel μ receptor G protein Pathway Selective modulator (μ-GPS) that differentially activates G protein coupling while greatly reducing β-arrestin recruitment. The prevalence of prospectively defined hypoventilation events with oliceridine vs morphine was analyzed in a randomized, double-blind, adaptive patient-controlled analgesia (PCA) phase 2b study. Patients (N=200) with moderate-to-severe acute postoperative pain following abdominoplasty were randomized to PCA regimens of intravenous oliceridine (1.5mg loading dose followed by either 0.1mg or 0.35mg demand doses), placebo, or morphine (4mg loading dose followed by 1mg demand doses), in a 1:1:1:2 ratio. All treatment groups used a 6-minute lockout interval. Oliceridine administration was associated with a significantly lower percentage of patients with hypoventilation events (15% and 31% with 0.1mg and 0.35mg, respectively) than the morphine group (53%; p<0.0005 and p<0.05, respectively). Other OAREs were generally less frequent in the oliceridine groups compared to morphine, and there were no drug-related serious adverse events reported in the study. The results of this study suggest that oliceridine may have an improved respiratory safety profile compared to conventional parenteral opioids. This study was supported by Trevena, Inc.

(433) Rapid reduction in pain intensity with oliceridine (TRV130), a novel μ receptor G protein Pathway Selective modulator (μ-GPS), vs. Morphine: an analysis of two phase 2 randomized clinical trials. E Viscusi, H Minkowitz, L Webster, D Soergel, D Burt, R Subach, and F Skobieranda; Premier Research Group, Austin, TX.

Opioids are widely employed for management of moderate-to-severe acute pain; however, opioid-related adverse events (OAREs), including respiratory depression and gastrointestinal effects, are important and may limit dosing required for analgesic efficacy. Conventional opioids bind to μ-opioid receptors and non-selectively activate two intracellular signaling pathways: G protein coupling, linked to analgesia, and β-arrestin recruitment, linked to OAREs and limiting efficacy. Oliceridine (TRV130) is a novel μ receptor G protein Pathway Selective modulator (μ-GPS) that differentially activates G protein coupling while mitigating β-arrestin recruitment. Here we examine speed of early reduction in pain intensity with oliceridine vs. morphine from two phase 2 studies: a randomized, double-blind, adaptive phase 2a study in patients (N=339) experiencing postoperative pain following bunieronectomy; and a randomized, double-blind, adaptive controlled adaptively designed phase 2b study in patients (N=200) following abdominoplasty. In the bunionectomy study, pain intensity differences (PID) at 5 minutes were -4.1 and -5.8 after oliceridine 2mg and 3mg, respectively, compared