(400) First-in-man evaluation of PF329, a abuse-resistant prodrug of hydromorphone

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PF329, an abuse- and tamper-resistant prodrug of hydromorphone, is being developed by PharmacoFore for treatment of chronic pain. When administered orally, PF329 is cleaved by gastrointestinal trypsin to hydromorphone and inactive fragments. PF329 is not active at the opioid receptor and does not convert to hydromorphone systemically. Unlike formulation approaches for abuse-resistance, PF329 is not affected by chewing or crushing. A first-in-man study was conducted in healthy, monitored, subjects at Nucleus Network Limited (Melbourne, Australia), with approval from their IRB. Part 1: 51 fasted subjects received a single oral dose of Dilaudid® (0.5-24 mg) or PF329 (1-48 mg). Part 2: 12 subjects received 16-mg PF329 either fasted or after a high-fat meal (crossover design). All doses were in solution. Subjects received naltrexone before (Part 1) and 12 hours after study drug administration (Parts 1, 2). Plasma was sampled for 72 hours and assayed for PF329, hydromorphone, and PF329 fragments. Hydromorphone Cp peaked < 1 hour following hydromorphone and at 3-4 hours following PF329; hydromorphone Cmax was markedly lower following PF329. With PF329, hydromorphone AUC was dose proportional; variability in dose-normalized Cp was low. Naltrexone did not affect hydromorphone AUC. A high-fat meal increased hydromorphone AUC 10%, but did not affect Cmax or Tmax. Population pharmacokinetic modeling indicated that 80% of PF329 was converted to hydromorphone (based on AUC); this fraction did not vary with PF329 dose. PF329 was detected in most subjects but reached assay LOQ quickly; PF329 fragments were detected transiently. Adverse events were mild-moderate and consistent with exposure to hydromorphone and naltrexone. In summary, PF329 conversion to hydromorphone is dose-proportional over a broad range of doses, with low variability. Conversion to hydromorphone delays Tmax and decreases Cmax. Future clinical trials will confirm that PF329's hydromorphone time profile is efficacious in chronic pain. Supported by PharmacoFore, Inc.

(401) Assessing risk of alcohol-induced dose dumping with the use of a new extended-release hydrocodone formulation

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Extended-release opioid formulations may offer advantages relative to immediate-release forms by decreasing dosing frequency. However, the requirement for increased drug load introduces the need to protect against intentional or accidental dose dumping since the rapid release of active drug may cause increased toxicity. A new extended-release hydrocodone tablet has been developed that employs OraGuard technology, a novel platform that is intended to resist dose dumping when taken with alcohol or when pulverized. This randomized, open-label, crossover study assessed the effect of alcohol on the pharmacokinetics of this hydrocodone extended-release formulation. Healthy subjects were randomized to receive hydrocodone extended-release 15 mg (under fasting conditions) with 240 mL of water containing 0%, 4%, 20%, or 40% alcohol. Participants received each regimen once, separated by at least 5 days. Subjects received naltrexone to block opioid receptors. Blood samples for pharmacokinetics were collected pre-dose and through 72 hours post-dose. Pharmacokinetic parameters included peak plasma hydrocodone concentration (C_{max}) and area under the plasma hydrocodone concentration-versus-time curve to infinity ($AUC_{0-\infty}$). Safety was also assessed. Forty subjects were enrolled; 31 completed all 4 dosing/sampling periods and 30 were evaluable for at least 1 pharmacokinetic comparison. Geometric mean C_{max} with 0%, 4%, 20%, or 40% alcohol was 11.8-12.4, 13.2, 13.5, and 13.3 ng/mL and geometric mean $AUC_{0-\infty}$ was 186.3-192.8, 207.6, 219.7, and 212.9 ng•hr/mL, respectively. No appreciable differences in the shapes of the mean plasma hydrocodone concentration-versus-time profiles were observed when study drug was administered with up to 40% alcohol. No serious adverse events were reported; the incidence of adverse events increased with increasing concentrations of alcohol (25%, 57%, and 61% with 4%, 20%, and 40% alcohol, respectively). Hydrocodone extended-release tablets were resistant to dose dumping when administered with alcohol. Systemic exposures (C_{max} and AUC) were similar with (4-40%) and without alcohol. Sponsored by Cephalon, Inc.

(402) Early use of adherence tests and recognition of opioid misuse may lower cost of chronic pain treatment

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Chronic pain affects more than 45 million Americans, and is a major reason why millions seek medical attention each year. Chronic pain in the United States is associated with excessively high disease management costs, largely due to reduced productivity, compensation costs, and treatment of comorbid conditions. Opioid use in chronic pain has escalated in the past decade, increasing the risk for drug nonadherence and associated drug abuse, potential addiction, and aberrant drug-related behaviors (ADRBs). Accordingly, health care costs for treatment of drug abuse have risen, with opioid abusers 25 times more likely to require hospitalization than non-opioid abusers. These costs could be significantly curtailed by early detection of patient nonadherence, using urine drug tests (UDTs), which would enable more prompt recognition and treatment of controlled substance-related ADRBs, and drug addiction and abuse problems. Adherence in chronic pain may be determined by point-of-care (POC) immunoassays, and more sensitive laboratory urine tests employing gas chromatography/mass spectrometry with high-performance liquid chromatography tests (LUTs). Cost/benefit studies suggest that the cost of LUTs to optimize adherence may reduce costs associated with nonadherence, such as inpatient clinical care and patient self-release. Current estimates suggest appropriate use of LUTs could decrease the cost of chronic pain therapy as much as 14.8-fold. In order to realize optimal cost benefits of UDTs it essential that physicians are better educated on how to define and detect drug abuse, addiction, and diversion. There is also a need for physician education on the proper implementation of POCs and LUTs, and interpretation of adherence test data. Substantial cost savings could be achieved by early monitoring of drug adherence using POC and follow-up LUTs in nonadherent chronic pain patients, especially those taking opioid therapy. Supported by AIT Laboratories.

(403) Pharmacokinetics of abuse deterrent, extended release once-a-day dosage forms of levorphanol: a single-dose, 5-way crossover study

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Extended release (ER) opioid analgesics are widely utilized for the treatment of chronic pain unresponsive to non-opioid analgesics. Levorphanol is an analgesic with opioid agonism, monoaminergic reuptake inhibition and NMDA antagonism. The pharmacokinetics of levorphanol are poorly characterized. This study evaluated the pharmacokinetics of four novel abuse deterrent ER dosage forms of levorphanol versus immediate release (IR) levorphanol. Fifteen healthy subjects participated in this single-center, randomized, analytically masked, fasted five-way crossover study in the USA under naltrexone block. During each period, subjects received one dosage form of levorphanol ER or IR. Each subject received naltrexone in order to minimize the potential for levorphanol-related adverse effects. Twenty-one sequential blood samples were obtained during each dosing period over 48 hr. There was a 7-14 day washout period between each of the 5 dosing-periods. Plasma samples were analyzed using a fully validated and robust LC/MS/MS method. Pharmacokinetic parameters included: Cmax, Tmax, T1/2, AUClast, AUCinfinity and apparent oral clearance. Data were analyzed by non-compartmental methods. The analytical method had an intra-run and inter-run CV of 0.9% to 6.0% and 3.3% to 4.7%, respectively. The elimination kinetics of oral levorphanol showed minimal variability, with a CV of 12.8%. All 4 levorphanol ER dosage forms provided robust ER characteristics suitable for once-a-day dosing. For the levorphanol ER dosage forms, the mean Tmax ranged from 9.15 to 12.29 hr vs. 2.40 hr for IR; the ratio (%) of dose normalized ER to IR Cmax ranged from 26.7% to 40.9%; and the ratio of dose normalized ER to IR AUCinfinity ranged from 82.16% to 99.27%. The mean apparent oral clearance was 93.14 L/h. Levorphanol ER provided robust extended-release characteristics suitable for once-a-day dosing. Supported by a grant from TheraQuest Biosciences, Inc.