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(392) Lack of correlation between the dose of fentanyl sublingual spray for breakthrough cancer pain and the dose of around-the-clock opioid for persistent pain

S Nalamachu, R Rauck, L Dillaha, and N Parikh; INSYS Therapeutics, Phoenix, AZ

Fentanyl sublingual spray is indicated for the treatment of breakthrough cancer pain (BTCP) in opioid-tolerant patients. This analysis evaluated the correlation between the dose of around-the-clock (ATC) opioid for persistent pain and effective dose of fentanyl sublingual spray for BTCP during the 26-day open-label portion of a phase 3, randomized, placebo-controlled trial. Adult opioid-tolerant patients with 1-4 episodes of BTCP were titrated to a dose of sublingual fentanyl spray (100, 200, 400, 600, 800, 1200, or 1600 mcg) that provided effective analgesia for 2 consecutive BTCP episodes. Of the 130 patients who received fentanyl sublingual spray, 98 (75.4%) completed the titration period. For those achieving successful titration , opioids used for ATC pain management at baseline included oxycodone/oxycodone hydrochloride (75.8%), morphine/morphine sulfate (41.1%), fentanyl/fentanyl citrate (40.0%), hydrocodone/hydrocodone acetaminophen (32.6%), hydromorphone/hydromorphone hydrochloride (31.6%), and methadone/methadone hydrochloride (13.7%). For BTCP, 93.5% (n=86) of patients reported using only oral opioids at baseline; commonly reported medications included hydromorphone hydrochloride (23%), oxycodone (22%), hydrocodone/acetaminophen (22%), and oxycodone/acetaminophen (16%). During the open-label phase, the median morphine equivalent dose of ATC opioid was 200.0 mg (range, 60.0-7545.0 mg). The median dose of fentanyl sublingual spray was 800 mcg and the most common doses were 800 mcg (24.5%) and 1200 mcg (20.4%). Based on the Spearman rank correlation, there was no clinical correlation observed between the successful dose of fentanyl sublingual spray for BTCP and ATC morphine equivalent dose (r=0.351, n=98). The lack of apparent correlation between ATC and BTCP dose underscores the importance of individual patient titration when determining an effective dose of fentanyl sublingual spray for BTCP. Technical editorial and medical writing assistance provided by Synchrony Medical Communications, LLC, funded by INSYS Therapeutics.

(393) Pharmacokinetics of hydrocodone following administration of single and multiple 90-mg doses of extended-release hydrocodone bitartrate formulated with OraGuard™ technology

M Darwish, M Bond, W Tracewell, and P Robertson; Cephalon, Inc., Frazer, PA

A novel extended-release hydrocodone tablet, formulated with OraGuard™ technology, is being developed. This study evaluated the pharmacokinetics and tolerability of single and multiple doses of 90 mg in healthy, naltrexone-blocked subjects. After IRB approval and written informed consent were obtained, subjects received a 90-mg dose in Period 1 (single dose). In Period 2 (multiple doses every 12 hours), subjects were titrated from 45 mg to 90 mg over 5 days then continued on 90 mg until day 10. Subjects also received 50-mg naltrexone every 12 hours. Plasma samples were collected before and over 72 hours after each study drug administration. Pharmacokinetic parameters included peak plasma drug concentration (C_{max}), area under the curve (AUC) from time 0 to the time of last measurable drug concentration (AUC_{0-t}), AUC from time 0 to 12 hours after a single dose (AUC_{0-12}), AUC for 1 dosing interval after multiple doses (AUC_{τ}), terminal elimination half-life ($t_{1/2}$), and observed (R_{obs}) and steady-state accumulation (R_{ss}) ratios. Tolerability also was assessed. Thirty-three of 40 enrolled subjects completed the study. Mean values after single and multiple doses were: C_{max} 56.4 and 123.1 ng/mL, AUC_{0-t} 1064 and 2453 ng•h/mL, and $t_{1/2}$ 9.9 and 10.7 hours, respectively. Mean AUC_{0-12} after a single dose was 462 ng•h/mL, and mean AUC_{τ} after multiple doses was 1282 ng•h/mL. Mean R_{obs} was 2.8 and mean R_{ss} was 1.2. No serious adverse events were reported. Five subjects discontinued due to adverse events. The pharmacokinetic profile of hydrocodone was qualitatively similar after single and multiple 90-mg doses and is consistent with that observed after multiple dosing of 45 mg every 12 hours in a previous study. Mean hydrocodone exposure was 2.8-fold higher at steady state than after a single dose. Extended-release hydrocodone was well tolerated by the naltrexone-blocked subjects in this study.

(394) Selection of a hydrocodone bitartrate extended-release prototype with optimal tamper resistance and extended-release characteristics

M Darwish, M Bond, P Robertson, and W Tracewell; Cephalon, Inc., Frazer, PA

Hydrocodone is available only in immediate-release (IR) combination products for treatment of pain in the United States. This randomized, open-label, crossover study intended to identify a prototype with the highest tamper resistance, which maintains optimal extended-release (ER) characteristics. Pharmacokinetic profiles were characterized for 3 ER hydrocodone prototypes designed to be resistant to rapid release of drug upon product tampering. After IRB approval and informed consent were obtained, healthy subjects were randomized. During the study, subjects received a single 45-mg dose of each of the 3 ER hydrocodone prototypes (with relatively low, intermediate, or high levels of OraGuard™ coating). There was a minimum 5-day washout between hydrocodone doses. Subjects received naltrexone before and after each dose of study medication to block opioid receptors and minimize opioid-related adverse events. Blood samples for pharmacokinetics were collected before and over 72 hours after each study drug administration. Measures included peak plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the curve from time 0 to infinity ($AUC_{0-\infty}$), and terminal elimination half-life ($t_{1/2}$). Safety also was assessed. Forty subjects enrolled; 37 completed the study. Mean values for the low-, intermediate-, and high-coating ER hydrocodone prototypes were: C_{max}, 49.2, 32.6, and 28.4 ng/mL; $AUC_{0-\infty}$, 640.0, 600.3, and 577.8 ng•hr/mL; and $t_{1/2}$, 11.7, 11.4, and 11.3 hours, respectively. Median t_{max} values were 5.9, 7.9, and 8.5 hours, respectively. The incidence of adverse events was similar between the low- (16%), intermediate- (13%), and high-coating (24%) ER hydrocodone prototypes. No serious adverse events were reported. Each hydrocodone prototype demonstrated ER characteristics with plasma levels being maintained over the full intended 12-hour dosing interval. The high-coating ER hydrocodone prototype was selected for further development because of its potential to better resist rapid release of drug upon product tampering.

(395) Evaluation of the abuse potential of an extended release hydrocodone bitartrate tablet formulated with OraGuard™ technology in non-dependent, recreational opioid users

M Darwish, M Bond, W Tracewell, and P Robertson; Cephalon, Inc., Frazer, PA

This study examined the relative abuse potential of crushed and intact extended-release (ER) hydrocodone bitartrate tablets formulated with OraGuard™ technology as compared to immediate-release (IR) hydrocodone. Healthy adult subjects with a history of recreational opioid use who were not dependent on opioids were enrolled. After confirming that eligible subjects were able to tolerate a 45 mg dose of IR hydrocodone and differentiate the effects of hydrocodone from placebo, subjects were randomized to the double-blind crossover portion of the study in which abuse potential was assessed. Subjects received each of the following (one in each period with a 14-day washout between doses): intact 45 mg ER hydrocodone tablet, crushed 45 mg ER hydrocodone tablet, 45 mg IR hydrocodone powder in a noncarbonated beverage, and placebo. Relative abuse potential was assessed by a series of tests. The primary endpoint was maximum effect (E_{max}) of drug liking based on question 1 of the Drug Liking and Effects Questionnaire (DLEQ). Overall Drug Liking Visual Analog Scale (VAS) was a secondary endpoint. Safety and tolerability was assessed throughout the study. Forty-two subjects were enrolled into the relative abuse potential assessment. Intact ER hydrocodone demonstrated significantly lower drug liking compared with IR hydrocodone based on DLEQ E_{max} (53.9 vs. 85.2; $p<0.001$) and Overall Drug Liking VAS (49.2 vs. 75.0; $p<0.001$). Crushed ER hydrocodone also demonstrated significantly lower drug liking compared with IR hydrocodone when assessed by both measures (DLEQ E_{max} 66.9 vs. 85.2, $p<0.001$, and Overall Drug Liking VAS 59.0 vs. 75.0, $p<0.001$). Outcomes for other secondary measures were consistent with these results, suggesting that ER hydrocodone, either intact or crushed, may have a lower abuse potential compared to IR hydrocodone. No new safety signals were observed with ER hydrocodone and there were no serious adverse events during the study.