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A Single Accelerating Dose Study to Evaluate Safety and Pharmacokinetics (PK) of FV-100 in Healthy Subjects

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Background: FV-100 is a 5′-valyl prodrug of CF-1743, a highly potent oral bicyclic nucleoside analogue, in development for the treatment of herpes zoster, or shingles. *In vitro* studies have demonstrated that CF-1743 rapidly enters varicella zoster-infected cells and can completely stop viral replication within 4 h of exposure. This study assessed the safety and PK of FV-100 in 24 healthy subjects after a single oral dose.
Methods: Subjects were randomized into three sequential ascending oral dose cohorts: 10 mg, 20 mg, and 40 mg. In each cohort, six subjects received FV-100 and two received placebo. Plasma for PK analysis was obtained immediately pre-dose and at 15 min, 30 min and 45 min, and 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h after dosing. Safety data from all subjects in each cohort was reviewed when subjects completed the Study Day 15 evaluation. Advancement to the next cohort occurred after pre-determined safety criteria were met.
Results: No serious adverse events were observed. A total of four subjects reported seven adverse events (AEs) thought by the investigator to be possibly related to study drug (two headache, one hematuria, one flank tenderness, one flatulence, one increased bowel movements). All AEs were mild and resolved within the study period. There were no clinically significant changes in vital signs, serum chemistries, hematology, and electrocardiograms obtained throughout the trial. Non-compartmental PK analysis indicated that the Cmax was 1.81 ng/ml, 2.83 ng/ml, and 13.5 ng/ml for the 10 mg, 20 mg, and 40 mg doses, respectively. The 40 mg dose resulted in levels of CF-1743 that exceeded the EC_{50} for >8 h.
Conclusions: Single oral doses of FV-100 ranging from 10 mg to 40 mg were generally well tolerated in this study. The PK profile suggests rapid conversion from FV-100 to CF-1743, with levels that exceed the EC_{50}. Taken together these data support proceeding to additional clinical studies to evaluate increased single oral doses as well as multiple ascending doses in healthy subjects.

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Single-Dose Safety and Pharmacokinetics of ST-246, A Novel Orthopoxvirus Egress Inhibitor

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ST-246 is a novel, potent orthopoxvirus egress inhibitor that is being developed to treat pathogenic orthopoxvirus infections of humans. A phase I, double-blind, randomized, placebo-controlled single ascending dose study was conducted to determine safety, tolerability, and pharmacokinetics of ST-246 in healthy volunteers. ST-246 was administered as capsules in single oral doses of 500, 1000, and 2000 mg to fasting healthy volunteers and 1000 mg to non-fasting healthy volunteers. ST-246 was well tolerated with no severe adverse events (AEs) or serious adverse events (SAEs), and no subject was withdrawn due to drug treatment. The most commonly reported AE was transient neutropenia that was determined to be an artifact of testing and was more common in placebo recipients then in ST246 subjects. ST-246 was readily absorbed following oral administration with mean times to maximum plasma concentration from 2 to 3 h and exhibited dose linearity in the plasma exposure for the dose range of 500–2000 mg. Absorption was greater in non-fasting volunteers compared to fasting volunteers. Administration of ST-246 at 500 mg resulted in exposure levels sufficient for inhibiting orthopoxvirus replication when compared to exposure levels in non-human primates administered a dose of 10 mg/kg (200 mg human equivalent, based upon body surface area calculations) in which ST-246 protected animals from lethal orthopoxvirus infection.

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