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Pharmacokinetics and Safety of FV-100, a Novel Oral Anti-Herpes Zoster Nucleoside Analogue, Administered in Single and Multiple Doses to Healthy Young Adult and Elderly Adult Volunteers[▽]

Helen S. Pentikis,[1] Mark Matson,[2] George Atiee,[3] Brian Boehlecke,[4] Jeff T. Hutchins,[5] Joseph M. Patti,[5] Geoffrey W. Henson,[5]* and Amy Morris[5]†

SAJE Consulting LLC, 1101 East 33rd Street, Suite C310, Baltimore, Maryland 21218[1]; Prism Research, Inc., 1000 Westgate Dr., Suite 149, St. Paul, Minnesota 55114[2]; ICON Development Solutions, 8307 Gault Lane, San Antonio, Texas 78209[3]; Rho, Inc., 6330 Quadrangle Drive, Suite 500, Chapel Hill, North Carolina 27517[4]; and Inhibitex, Inc., 9005 Westside Parkway, Alpharetta, Georgia 30009[5]

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FV-100 is the prodrug of the highly potent anti-varicella zoster virus bicyclic nucleoside analogue CF-1743. To characterize the pharmacokinetics and safety of oral FV-100, 3 randomized, double-blind, placebo-controlled clinical trials were conducted: (i) a single-ascending-dose study in 32 healthy subjects aged 18 to 55 years (100-, 200-, 400-, and 800-mg doses) with an evaluation of the food effect in the 400-mg group; (ii) a multiple-ascending-dose study in 48 subjects aged 18 to 55 years (100 mg once daily [QD], 200 mg QD, 400 mg QD, 400 mg twice a day, and 800 mg QD for 7 days); and (iii) a 2-part study in subjects aged 65 years and older with a single 400-mg dose in 15 subjects and a 400-mg QD dosing regimen for 7 days in 12 subjects. FV-100 was rapidly and extensively converted to CF-1743, the concentration of which remained above that required to reduce viral activity by 50% for the 24-hour dosing period. Renal excretion of CF-1743 was very low. A high-fat meal reduced exposure to CF-1743; a low-fat meal did not. Pharmacokinetic parameters for the elderly subjects were comparable to those for the younger subjects. FV-100 was well tolerated by all subjects. The pharmacokinetic and safety profiles of FV-100 support its continued investigation for the treatment of herpes zoster and prevention of postherpetic neuralgia with once-daily dosing and without dose modifications for elderly or renally impaired patients.

Herpes zoster (HZ), or shingles, is a painful rash caused by varicella zoster virus (VZV) infection of peripheral nerves. It has the highest incidence of all neurological diseases, with over 1 million cases developing annually in the United States (5, 8). The Centers for Disease Control and Prevention reports that 32% of people in the United States will experience zoster during their lifetimes, and as many as 50% of those living until 85 years of age will develop shingles (5, 14).

HZ is caused by the reactivation of latent VZV residing in ganglia in persons with prior chicken pox with subsequent spread to the peripheral nerves. While the acute rash generally heals within 2 to 4 weeks, the most distressing symptom of HZ is pain, both acute and chronic. Chronic pain associated with HZ infection is also referred to as postherpetic neuralgia (PHN), a clinically significant condition that can last from several months to years. Several clinical trials of antiviral medications now approved for the treatment of HZ as well as meta-analyses have shown a reduction in acute pain and PHN with antiviral medication treatment compared to placebo (7, 8, 15). However, 22% of all patients with HZ still develop PHN (2), and thus, existing interventions, including vaccination and analgesia as well as currently approved antivirals, do not completely prevent or adequately treat all cases of HZ pain and PHN (4, 6, 13, 16). Development of more effective compounds for the prevention and treatment of HZ-associated pain is an unmet medical need (3).

A number of *in vitro* tests were conducted to evaluate the potential toxicity of FV-100 (Fig. 1) and CF-1743. More specifically, genotoxicity (bacterial reverse mutation, mouse lymphoma, and mouse bone marrow erythrocyte micronucleus) studies were negative for FV-100 and CF-1743. *In vitro* cytotoxicity studies in normal human primary hepatocytes, keratinocytes, and rapidly dividing HepG2 cells, demonstrated mean 50% cytotoxic concentration values of >10 μM. Furthermore, FV-100 and CF-1743 exhibited no suppressive effect on mitochondrial activity (as measured by mitochondrial/nuclear DNA ratios) in rapidly dividing leukemic lymphoid (CEM) cells.

The nonclinical toxicology of FV-100 and CF-1743 has been characterized in a variety of good laboratory practices studies that included single-dose and repeat-dose (14 days of dosing followed by a 14-day recovery) toxicity studies in rats and dogs, an *in vivo* telemetry study of the cardiovascular effects of FV-100 after oral dosing in dogs, as well as respiratory function and neuropharmacological profiling following oral doses in rats. In the single-dose studies and the repeat-dose studies, the no-observed-adverse-effect levels (NOAELs) for the rats and dogs were approximately 1 g and 3.3 g human dose equivalents, respectively. The *in vivo* telemetry study of the cardiovascular effects following oral dosing of up to 100 mg/kg of body weight FV-100 in dogs produced no measurable effects on cardiac

* Corresponding author. Mailing address: Inhibitex, Inc., 9005 Westside Parkway, Alpharetta, GA 30009. Phone: (678) 746-1182. Fax: (678) 746-0626. E-mail: ghenson@inhibitex.com.
† Present address: IND 2 Results LLC, 856 Drewry Street, Atlanta, GA 30306.
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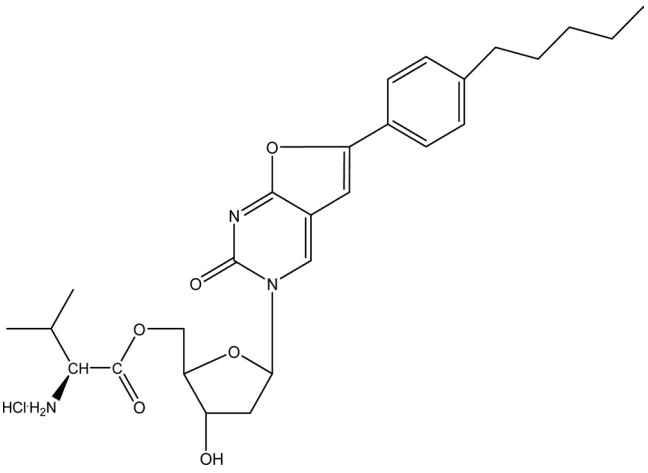

FIG. 1. Structure of FV-100.

rhythm, electrocardiogram (ECG) morphology, or circulatory functions. Finally, oral administration of FV-100 (50-, 100-, and 500-mg/kg doses) in rats did not induce biologically relevant respiratory changes or any apparent neuropharmacological effects.

Overall, the *in vitro* and *in vivo* safety and pharmacokinetic (PK) profiles of FV-100 and CF-1743 developed from nonclinical testing clearly supported the progression into human clinical trials.

After a pilot study in which human subjects received single low oral doses (10, 20, and 40 mg) of FV-100 and in which FV-100 exhibited a favorable safety profile, 3 additional studies were conducted from April 2008 to January 2009 to more fully characterize the pharmacokinetics and evaluate the safety of potential therapeutic doses of FV-100. These randomized, double-blind, placebo-controlled clinical trials were conducted in accordance with good clinical practices, the Declaration of Helsinki (October 2000), and United States Food and Drug Administration regulations, as codified in the *Code of Federal Regulations*, Title 21, including approval of the protocol and written informed consent form by an institutional review board before study initiation and the collection of informed consent prior to screening of each subject.

MATERIALS AND METHODS

Study subjects, designs, and treatments. Healthy male and female subjects aged 18 to 55 years were enrolled in 2 trials: 32 subjects in study INH-FV1-002 and 48 subjects in study INH-FV1-003. Key eligibility criteria for these studies were normal laboratory tests, no clinically significant abnormalities on ECG, weight of ≥50 kg, body mass index of 19 to 30, no active medical problems, no history of cardiac disease, no history of renal insufficiency or progressive renal disease, and no use within 2 weeks prior to dosing of medications known to have renal toxicity or known to increase the QTc duration. Study INH-FV1-002 evaluated single oral doses of FV-100 at 100, 200, 400, and 800 mg as well the effect of food (a standard high-fat meal and a standard low-fat meal) in the same cohort of subjects who had received the 400-mg dose without food; a minimum of 28 days separated each single dose. Both meals were as follows and were consumed within 30 min prior to dosing. The standard high-fat meal consisted of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 oz hash browns, and 8 oz whole milk. The standard low-fat meal consisted of 2 slices of toast, 1 cup of applesauce, and 8 oz 1% milk.

INH-FV1-003 evaluated oral doses of FV-100 at 100, 200, 400, and 800 mg given once daily (QD) for 7 days and 400 mg of FV-100 given every 12 h (q12h) for 7 days.

After completion of the study with the 400-mg cohort in the single-dose study of subjects aged 18 to 55 years, 15 elderly male and female subjects ≥65 years of age were enrolled in the first cohort of study INH-FV1-004 and received single oral doses of 400 mg FV-100. After completion of the study with the 400-mg once-daily cohort in the multiple-dose study in the younger group, a second cohort of 12 elderly male and female subjects was enrolled in study INH-FV1-004 and received 400 mg FV-100 once daily for 7 days. Key eligibility criteria for this study were the same as those for the young subjects, except that rather than excluding subjects with any active medical problem, only subjects with an acute medical problem for which there had been evaluation or treatment within 30 days of the study were excluded and that rather than excluding subjects with a history of any cardiac disease, only subjects with a history of clinically significant cardiac disease were excluded. Pharmacokinetic and safety data from this study were compared with data from the younger subjects who had received the same doses.

The studies were conducted at Prism Research, Inc. (St. Paul, MN), and ICON Development Solutions (San Antonio, TX) clinical research units. In each of the 3 studies, a computer-generated list available only to a designated pharmacist at each site was used for randomization. Treatment assignment was double blinded; active FV-100 and placebo were formulated as opaque gelatin capsules identical in appearance and weight.

Subjects in single-dose cohorts were randomized to FV-100 or placebo in a 6:2 ratio (cohort aged 18 to 55 years) and in a 10:2 ratio (elderly cohort). They remained in the research unit from 12 h prior to the single dose until 24 h after dosing for observation and PK sampling and returned on study days 3, 4, 7, and 15 for additional safety evaluations. Escalation to the next higher dose occurred after safety and PK data from all subjects within a dose cohort through study day 15 were reviewed.

Subjects in multiple-dose cohorts were randomized to FV-100 or placebo in a 6:2 ratio (cohort aged 18 to 55 years) and in a 10:2 ratio (elderly cohort) and received study drug for 7 days. They remained in the research unit from 12 h prior to the single dose until 24 h after dosing for observation and PK sampling on study days 1 and 7 and returned on study days 3, 4, 5, 6, 9, 10, 11, and 22 for additional PK and safety evaluations. In study INH-FV1-003, escalation to the next higher dose occurred after safety data from all subjects in a cohort through study day 22 were reviewed.

Pharmacokinetic sample collection and assays. Plasma and urine samples for PK analysis were collected according to the schedule shown in Table 1.

Concentrations of FV-100 and CF-1743 in EDTA-anticoagulated plasma were determined at MedTox Laboratories (St. Paul, MN) using a validated high-performance liquid chromatography–positive electrospray ionization tandem mass spectrometry assay (HPLC-ESI+MS/MS) and a cross-validated ultraperformance liquid chromatography (UPLC)–positive electrospray ionization tandem mass spectrometry assay (UPLC-ESI+MS/MS). In both assay systems, FV-100 and CF-1743 were analyzed over the range of 200 to 100,000 pg/ml using a structural analogue, CF-1712, as an internal standard. Briefly, 200 μl of EDTA-anticoagulated plasma was mixed with 25 μl of a solution containing CF-1712 and 20 μl of 5.0% trifluoroacetic acid. Samples were then diluted with 400 μl of

TABLE 1. Schedules of sample collection for pharmacokinetic study[a]

Sample and day	Single-dose-cohort studies INH-FV1-002 and INH-FV1-004	Multiple-dose-cohort studies INH-FV1-003 and INH-FV1004	
		QD cohort	q12h cohort
Plasma			
Day 1	A	B + D	C + D
Day 7	NA	A	E
Urine			
Day 1	F	G	G
Day 7	NA	F	F

[a] A, predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 20, 24, 48, and 72 h postdose; B, predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 20 h postdose; C, predose and 0.5, 0.75, 1, 1.5, 2, 4, 8, 10, 12, 12.5, 12.75, 13, 13.5, 14, 16, and 20 h post-morning dose; D, prior to dose on days 2, 3, 4, 5, and 6; E, predose and 0.5, 0.75, 1, 1.5 2, 4, 8, 10, 12, 12.5, 12.75, 13, 13.5, 14, 16, 20, 24, 48, 72, and 96 h post-morning dose; F, 0 to 1, 1 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, and 48 to 72 h postdose; G, 0 to 1, 1 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 h postdose; NA, not applicable.

TABLE 2. Schedules of safety procedures

Procedure	Single-dose-cohort studies INH-FV1-002 and INH-FV1-004	Multiple-dose-cohort studies INH-FV1-003 and INH-FV1-004
Physical exam	Predose in study INH-FV1-004 only Study days 2, 4, 8, 15	Predose in study INH-FV1-004 only Study days 2, 4, 8, 11, 22
Vital sign determination	Predose Frequently on study days 1 to 2 Once on study days 3, 4, 8, 15	Predose Frequently on study days 1 to 2 and study days 7 to 8 Once on study days 4, 11, 22
ECG	Predose 1, 2, 4 h postdose Study day 15	Predose on study days 1 and 7 (3 ECGs performed) 1, 2, 4, 8, 12 h postdose on study days 1 and 7 Study day 22
Clinical sample lab analysis	Predose Study days 2, 4, 8, 15	Predose Study days 2, 4, 8, 11, 22

acetonitrile with 0.1% formic acid and clarified by vortex mixing, freezing, and centrifugation. The supernatant was analyzed as follows: (i) by HPLC-ESI+MS/MS using an isocratic mobile phase of 62% 0.1% formic acid and 38% acetonitrile with 0.1% formic acid with a flow rate of 700 μl/min through a 3.5-μm Agilent Zorbax SB-phenyl column (2.1 by 100 mm; Wilmington, DE) and an injection volume of 15 μl and (ii) by UPLC-ESI+MS/MS using an isocratic mobile phase of 52% 0.1% formic acid and 48% acetonitrile with 0.1% formic acid with a flow rate of 500 μl/min through a 1.8-μm Waters UPLC HSS T3 column (2.1 by 50 mm; Milford, MA) and an injection volume of 7 μl.

FV-100 was quantified by monitoring and summing the 2 transitions 498.5 > 216.0 and 498.5 > 188.1 *m/z*, and CF-1743 was quantified by monitoring the transition 399.1 > 283.1 *m/z*. CF-1712 was monitored using the transition 427.3 > 310.9 *m/z*. The assay was linear over the range of quantification for both analytes in all studies. The assays used for the quantification of FV-100 and CF-1743 were validated according to International Conference on Harmonisation guidelines. For FV-100, the coefficient of variation (CV) for interrun assays using the UPLC method ranged from 5.8% to 8.8%, and for intrarun assays, the CV ranged from 5.1% to 6.9%. For CF-1743, the CV for interrun assays ranged from 3.3% to 6.8%, and for intrarun assays, the CV ranged from 2.9% to 6.0%. Similar ranges of CV were observed for both assays. Concentrations of FV-100 and CF-1743 in urine were also determined at MedTox Laboratories using a UPLC-ESI+MS/MS assay with the same analysis range and internal standard. Briefly, 2.5 ml of acetonitrile was added to the urine sample (typically, 10 ml) and the mixture was vortexed. Since the collection volume of the urine samples was not rigorously controlled, d_5-propoxyphene was incorporated into the acetonitrile as a reference standard to determine the amount that the urine sample was diluted by the acetonitrile. A 200-μl aliquot of this mixture was mixed with 20 μl of CF-1712 and 20 μl of 5.0% trifluoroacetic acid. Aliquots were then diluted with 300 μl of acetonitrile with 0.1% formic acid and clarified by vortex mixing and centrifugation. The supernatant was analyzed via UPLC-ESI+MS/MS using an isocratic mobile phase of 52% 0.1% formic acid and 48% acetonitrile with 0.1% formic acid with a flow rate of 500 μl/min through a 1.8-μm Waters UPLC HSS T3 column (2.1 by 50 mm; Milford, MA) and an injection volume of 7 μl. FV-100 was quantified by monitoring the transition 498.5 > 216.0 *m/z*, and CF-1743 was quantified by monitoring the transition 399.1 > 283.1 *m/z*. CF-1712 was monitored using the transition 427.3 > 310.9 *m/z*, and d_5-propoxyphene was quantified using the transition 345.3 > 58.3 *m/z*. The assay was linear over the range of quantification for both analytes in all studies. In urine, for FV-100, the CV for the interrun assay ranged from 3.4% to 5.4%, and for intrarun assays, the CV ranged from 2.7% to 7.2%. For CF-1743, the CV for interrun assays ranged from 3.3% to 6.8%, and for intrarun assays, the CV ranged from 2.4% to 2.8%.

Pharmacokinetic modeling methods. SAJE Consulting (Baltimore, MD) analyzed the plasma concentration-time curve data for FV-100 and CF-1743 by noncompartmental methods using WinNonlin professional edition, version 5.2 (Pharsight Corp., Mountain View, CA), to obtain values for the following PK parameters as applicable and as appropriate for each study: peak (maximum) observed plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), area under the plasma concentration-time curve (AUC) from immediately prior to dosing (time zero) to time of last measurable plasma concentration (AUC_{0-last}) as well as over the 12-hour dosing interval (AUC_{τ}) and extrapolated to infinity ($AUC_{0-\infty}$), accumulation ratio (R_{obs}; which is equal to $AUC_{\tau,\ day7}/AUC_{\tau,\ day\ 1}$), apparent elimination half-life ($t_{1/2}$), apparent oral volume of distribution at the terminal phase (V_z/F), apparent systemic clearance (CL/*F*), apparent systemic clearance at steady state (CL_{ss}/F), amount of drug excreted unchanged in the urine over 72 h after a single dose (Ae_{0-72}), amount of drug excreted unchanged in the urine over 24 h on day 1 and 96 h on day 7 in multiple-dose cohorts (Ae_{0-24} and Ae_{0-96}, respectively), renal clearance (CL_R), and fraction of drug excreted unchanged in urine (*Fe*). Actual sampling times were used for the calculation of PK parameters, and nominal sampling times were used for the mean concentration-time figures. All calculations were based on nonmissing plasma concentrations.

Safety assessments. Subjects were screened within 21 days prior to the first dose, and each subject was evaluated for eligibility on the basis of medical history, medication use, physical examination, vital signs (blood pressure, heart rate, respiratory rate, and temperature) measured after the subject was supine for 3 min, 12-lead ECG obtained after the subject was supine for 5 min, and laboratory tests. Laboratory tests at screening were HIV and hepatitis serology, urine drug screen, pregnancy (in female subjects aged 18 to 55 years), hematology, serum chemistry, and urinalysis. Safety was subsequently monitored from physical examinations, vital signs, ECGs, laboratory tests (hematology, serum chemistry, and urinalysis), and assessment of adverse events (AEs) and concomitant medications.

Physical examinations, vital signs, ECGs, and laboratory tests were conducted at the time points detailed in Table 2. In study INH-FV1-002, a board-certified cardiologist measured the RR and QT intervals for each ECG manually and calculated a corrected QT interval using both Bazett's (QTcB) and Fridericia's (QTcF) formulae. Bazett's formula is $QTcB = QT/RR^{1/2}$, and Fridericia's formula is $QTcF = QT/RR^{1/3}$. QT_CX equal to B or F is the QT interval corrected for heart rate, and RR is the interval from the onset of one QRS complex to the onset of the next QRS complex. In studies INH-FV1-003 and INH-FV1-004, ECGs were transmitted to a centralized reading center for manual adjudication of RR, PR, QRS, and QT intervals; calculation of QTcB and QTcF; and interpretation of morphology and other parameters. Information on AEs and concomitant medications were collected throughout each study. AEs were coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 10.1, and concomitant medications were coded using the World Health Organization Drug Dictionary, version 2007 Q3.

Statistical analyses. All statistical analyses in the 3 studies were descriptive. The population analyzed for safety in each study included all subjects who received any dose of study medication. The PK analysis population in each study included all subjects who had at least 1 measurable plasma FV-100 or CF-1743 concentration. All analyses were performed using SAS software, version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Subject disposition and demographics. In study INH-FV1-002, 32 subjects were enrolled as planned. One subject in the placebo group withdrew on study day 4 because he did not want to continue to provide blood samples, and the other 31 subjects completed the study. The 6 subjects who received

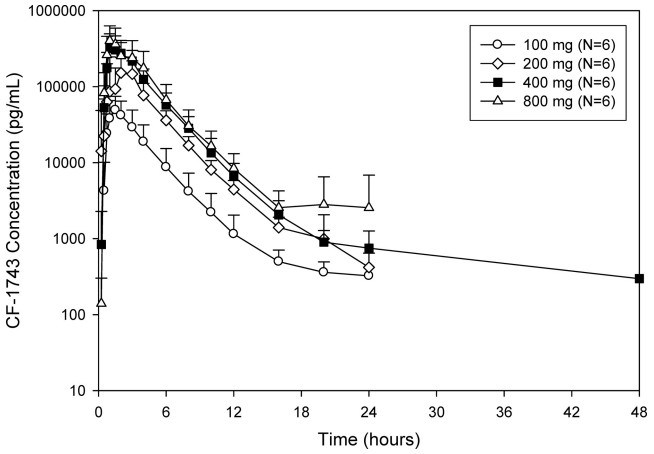

FIG. 2. Mean (with standard deviation) CF-1743 plasma concentration-time curves following administration of a single dose of FV-100 to healthy young volunteers (study INH-FV1-002).

active 400 mg FV-100 in the fasted period also completed the high-fat-meal period. Five of these subjects chose to enter and completed the low-fat-meal period that had been added in a protocol amendment.

It had initially been planned to enroll 40 subjects in study INH-FV1-003, but in order to better assess the variability in PK data between and among subjects, the study with the 200-mg QD cohort was repeated with 8 new subjects, resulting in a total of 16 subjects enrolled in the 200-mg QD cohorts and a total of 48 subjects in the study. One subject in the 200-mg QD group withdrew from the study on study day 1 prior to the 16-hour procedures, and 1 subject in the 400-mg QD group withdrew after dosing on study day 4; the other 46 subjects completed the study.

An additional 3 subjects were also added to study INH-FV1-004 to obtain more PK data. Thus, 15 rather than 12 subjects were enrolled in the single-dose cohort of this study; 13 subjects received FV-100, and 2 received placebo. Twelve subjects were enrolled in the multiple-dose cohort as planned, and all 27 subjects completed the study.

The mean ages of the young subjects in the single-dose and multiple-dose studies were 30 and 29 years, respectively, and the mean age of the elderly subjects in both the single-dose and multiple-dose parts of study INH-FV1-004 was 69 years. In these 4 groups, approximately 38%, 35%, 67%, and 25% of the subjects were female.

Single-dose pharmacokinetics in subjects aged 18 to 55 years. The mean CF-1743 concentration-time curves following a single administration of FV-100 to subjects aged 18 to 55 years are displayed by dose cohort in Fig. 2, and CF-1743 PK parameter estimates for single doses in both age groups are presented in Table 3. Rapid metabolism of FV-100 to CF-1743 was evident, with measurable concentrations of CF-1743 observed in plasma within 10 min of dosing. Mean maximum CF-1743 concentrations were observed at approximately 1.0 to 3.1 h following drug administration and indicate consistency in the rate of CF-1743 appearance in the plasma across dose groups. The mean rate (C_{max}) and extent ($AUC_{0-\infty}$) of exposure to CF-1743 ranged from 54,611 pg/ml to 508,108 pg/ml and 167,340 pg · h/ml to 1,381,083 pg · h/ml, respectively, over the 100-mg to 800-mg dose range. CF-1743 C_{max} and $AUC_{0-\infty}$ exhibited moderate to high variability, and a comparison across dose cohorts indicated a slight deviation from dose proportionality for these parameters over the dose range. The mean $t_{1/2}$ of CF-1743 was independent of dose and ranged from 3.1 to 4.5 h. Estimates of CL/*F* for CF-1743 ranged from 376 liters/h to 1,026 liters/h and are consistent with the rapid elimination of CF-1743 from plasma. In addition, V_z/F values for CF-1743 ranged from 1,629 liters to 3,683 liters over the dose range tested and suggest that CF-1743 may be widely distributed to peripheral tissues. The urinary excretion of CF-1743 was low for all dose cohorts, indicating that renal elimination is not likely to be an important pathway of elimination for CF-1743.

A high-fat meal decreased the CF-1743 C_{max} by approximately 87% and resulted in significant variability (CV = 82%) among individuals receiving FV-100 under high-fat fed conditions. The mean CF-1743 concentration-time curves following a single administration of FV-100 to subjects in the fast/fed study are shown in Fig. 3. Estimates of the CF-1743 AUC were reduced by 82% following concomitant administration of FV-100 with a high-fat meal. The low-fat meal did not have an impact on the CF-1743 C_{max} or AUC.

Multiple-dose pharmacokinetics in subjects aged 18 to 55 years. The mean CF-1743 concentration-time curves following the day 1 dose(s) and following the day 7 dose(s) of FV-100 to subjects aged 18 to 55 years are displayed by dose cohort in Fig. 4, and CF-1743 PK parameter estimates for multiple doses in both age groups are presented in Table 4. Rapid metabolism of

TABLE 3. Pharmacokinetic parameters for CF-1743 in plasma following administration of a single dose of FV-100[a]

Parameter	Study INH-FV1-002, young cohort				Study INH-FV1-004, elderly cohort, 400 mg (n = 13)
	100 mg (n = 6)	200 mg (n = 6)	400 mg (n = 6)	800 mg (n = 6)	
C_{max} (pg/ml)	54,611 (40)	225,711 (52)	424,115 (33)	508,108 (25)	211,515 (46)
T_{max} (h)	1.8 (1.0, 3.0)	2.5 (1.0, 3.0)	1.8 (1.0, 3.2)	1.3 (1.0, 3.0)	1.5 (1.0, 6.0)
$t_{1/2}$ (h)	3.1 (71.0)	4.5 (31)	3.2 (63)	3.2 (36)	8.2 (89)
AUC_{0-last} (pg · h/ml)	166,089 (50)	607,147 (41)	1,145,364 (27)	1,347,457 (37)	625,050 (45)
$AUC_{0-\infty}$ (pg · h/ml)	167,340 (56)	561,398 (44)	1,173,071 (29)	1,381,083 (40)	578,108 (42)
V_z/F (liters)	3,683 (83)	3,092 (79)	1,629 (66)	2,837 (37)	9,897 (92)
CL/*F* (liters/h)	1,026 (104)	470 (74)	376 (41)	662 (40)	906 (74)
Ae_{0-72} (mg)	0.0005 (24.2)	0.0020 (84.4)	0.0035 (76.4)	0.0047 (37.6)	0.0078 (61.3)
CL_R (liters/h)	0.0698 (14.4)	0.073 (103.4)	0.0718 (60.1)	0.0631 (49.4)	0.012 (41.8)
Fe (%)	0.0005 (66.2)	0.0010 (81.4)	0.0009 (75.4)	0.0006 (33.3)	0.002 (61.3)

[a] Data represent means (percent CVs) for all parameters except T_{max}, for which data are medians (minima, maxima).

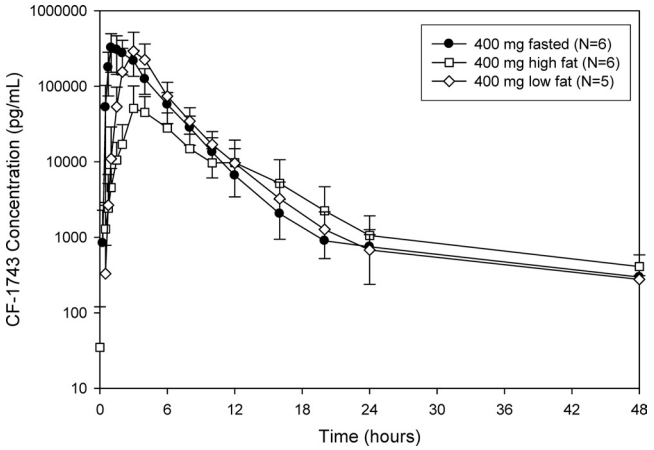

FIG. 3. CF-1743 plasma concentration-time curves following single-dose administration of 400 mg FV-100 to healthy young volunteers under fasted, low-fat-meal, and high-fat-meal conditions (study INH-FV1-002).

FV-100 to CF-1743 was evident following dosing on day 1 and on day 7, as CF-1743 concentrations were measurable in plasma within 15 to 30 min of dosing. The concentrations of CF-1743 were above the antiviral 50% effective concentration (EC_{50}) of 170 pg/ml for the entire 24-hour dosing interval following both single and multiple dosing. Following administration of doses on day 1 and day 7, the median T_{max} occurred at approximately 1.0 to 2.5 h across all treatment cohorts. The range of T_{max} estimates indicated a consistency across all cohorts and did not suggest significant variability in the rate of appearance of CF-1743 in plasma. C_{max} ranged from 59,167 pg/ml to 773,122 pg/ml following the first dose and 38,606 pg/ml to 735,123 pg/ml following 7 days of dosing. Exposure to CF-1743, as measured by AUC, ranged from 237,881 pg · h/ml to 1,624,948 pg · h/ml following the first dose and 112,513 pg · h/ml to 1,406,251 pg · h/ml following 7 days of dosing. C_{max} and AUC increased in a slightly greater than dose-proportional manner over the 100-mg to 800-mg dose range following administration of single and multiple doses.

The mean $t_{1/2}$ of CF-1743 was independent of dose and ranged from 2.8 to 6.1 h over the 100-mg to 800-mg dose range tested. The $t_{1/2}$ for CF-1743 was consistent for both single- and multiple-dose administration. Estimates of CL/*F* for CF-1743 ranged from 450 liters/h to 1,521 liters/h and are consistent with the rapid elimination of CF-1743 from plasma. V_z/F values ranged from 2,206 liters to 12,998 liters over the dose range tested for both single- and multiple-dose administration and suggest that CF-1743 may be widely distributed to peripheral tissues. The urinary excretion of CF-1743 was again low for all dose cohorts, indicating that renal elimination is not likely to be an important pathway of elimination for CF-1743.

Comparison of pharmacokinetics in young and elderly subjects. Figure 5 shows concentration-time curves for young and elderly subjects after 1 dose and after 7 daily doses of 400 mg FV-100. The PK parameters and associated variability of CF-1743 in young versus elderly subjects (Tables 3 and 4) indicated that the rates and extents of drug exposure were independent of the age of the subjects who received FV-100. It should be noted, however, that a trend toward slightly higher rates and extents of absorption was evident in younger subjects than elderly subjects following single-dose administration, whereas the opposite trend was evident following multiple-dose administration. CF-1743 concentrations were above the EC_{50} of 170 pg/ml for the entire 24-hour dosing interval in both young and elderly subjects.

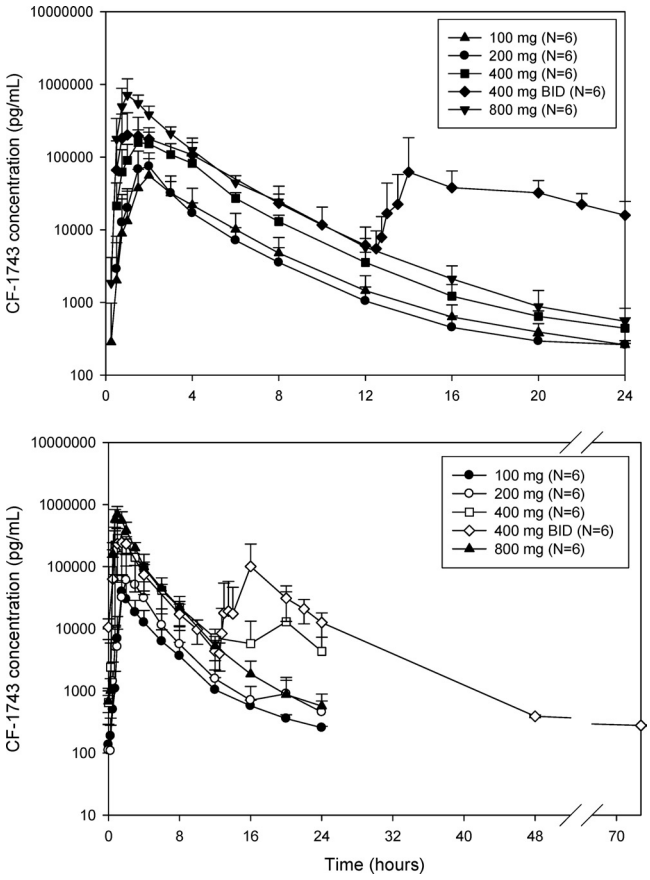

FIG. 4. Mean (with standard deviation) CF-1743 plasma concentration-time curves following administration of day 1 dose (top panel) and day 7 dose (bottom panel) of FV-100 to healthy young volunteers (study INH-FV1-003).

Safety. Single doses of FV-100 at potential therapeutic doses were well tolerated by subjects aged 18 to 55 years in study INH-FV1-002. There were few clinically significant changes observed in physical examinations, laboratory results, vital signs, and ECGs, and there were no trends observed in these parameters with increasing doses. Ten (41.7%) subjects who received FV-100 experienced 29 AEs, none of which were assessed to be definitely related to FV-100 and all of which were mild. The investigator assessed 12 of these events to be not related to FV-100 and 17 events to be possibly related to FV-100, but the assessment of the relationship of AEs to FV-100 showed that they were not dose dependent.

Safety results were similar when FV-100 was administered to subjects in the same age group in multiple doses over 7 days in study INH-FV1-003. Results from physical examinations, laboratory tests, vital signs, and ECGs did not indicate any additional toxicity related to multiple dosing. Twenty-one (52.5%) subjects experienced 49 AEs, all of which were mild. The

TABLE 4. Pharmacokinetic parameters for CF-1743 in plasma following day 1 and day 7 administration of FV-100[a]

Parameter	Day	INH-FV1-002, young cohort					INH-FV1-004, elderly cohort, 400 mg QD (n = 10)
		100 mg QD (n = 6)	200 mg QD (n = 6)	400 mg QD (n = 6)	400 mg q12h[b] (n = 6)	800 mg QD (n = 6)	
C_{max} (pg/ml)	1	59,167 (69)	93,453 (47)	189,524 (27)	273,760 (68)	773,122 (54)	428,412 (58)
T_{max} (h)		2.0 (1.5, 2.0)	1.8 (0.8, 2.0)	1.8 (1.0, 4.0)	1.3 (0.8, 2.0)	1.3 (1.0, 1.5)	1.5 (1.0, 3.0)
$t_{1/2}$ (h)		3.6 (23)	6.1 (126)	4.8 (74)	2.8 (40)	3.7 (10)	4.4 (13)
AUC_{0-last} (pg · h/ml)		170,979 (67)	182,013 (35)	570,956 (22)	1,177,498 (54)	1,544,208 (31)	1,135,815 (63)
$AUC_{0-\infty}$ (pg · h/ml)		237,881 (28)	184,616 (33)	540,100 (20)	1,764,033 (17)	1,624,948 (30)	1,192,944 (56)
V_z/F (liters)		2,256 (30)	12,998 (153)	6,037 (103)	2,910 (42)	2,794 (31)	2,637 (44)
CL/F (liters/h)		450 (32)	1,222 (42)	770 (24)	735 (34)	526 (27)	415 (45)
Ae_{0-24} (mg)		0.0015 (64.9)	0.0021 (37.8)	0.0085 (72.5)	0.0029 (64.3)	0.0222 (37.1)	0.0115 (53.1)
CL_R (liters/h)		0.0089 (31.7)	0.012 (14.1)	0.0117 (40.7)	0.0024 (34.8)	0.0168 (44.9)	0.011 (39.5)
Fe (%)		0.0015 (64.9)	0.0011 (37.8)	0.0021 (72.5)	0.0007 (64.3)	0.0028 (37.1)	0.0029 (53.1)
C_{max} (pg/ml)	7	38,606 (73)	80,666 (106)	342,658 (53)	329,325 (31)	735,123 (27)	590,932 (57)
T_{max} (h)		1.8 (1.5, 3.0)	2.5 (2.0, 4.0)	1.5 (0.8, 20.0)	1.8 (0.8, 2.0)	1.0 (0.8, 1.5)	1.5 (0.8, 2.0)
$t_{1/2}$ (h)		4.6 (48)	2.8 (44)	3.8 (20)	4.2 (64)	8.2 (89)	8.8 (59)
AUC_{0-24} (pg · h/ml)		111,134 (72)	204,768 (96)	947,557 (27)	1,219,357 (42)	1,498,849 (20)	1,617,353 (49)
$AUC_{0-\infty}$ (pg · h/ml)		112,513 (72)	242,149 (101)	1,034,797 (19)	1,220,762 (31)	1,406,251 (13)	1,655,793 (51)
R_{obs}		0.8 (55)	1.1 (66)	1.8 (29)	0.9 (20)	0.9 (10)	1.5 (39)
V_z/F (liters)		7,809 (58)	4,552 (44)	2,206 (37)	5,763 (40)	7,157 (99)	3,640 (70)
CL_{ss}/F (liters/h)		1,521 (87)	1,455 (45)	450 (30)	1,267 (51)	551 (19)	311 (57)
Ae_{0-96} (mg)		0.0013 (39.1)	0.0018 (91.6)	0.0168 (57.3)	0.0049 (101.7)	0.0193 (23.9)	0.0189 (61.0)
CL_R (liters/h)		0.0130 (39.5)	0.0108 (25.9)	0.0185 (25.2)	0.0026 (52.9)	0.0145 (34.5)	0.012 (29.5)
Fe (%)		0.0011 (62.4)	0.0009 (91.6)	0.0042 (57.3)	0.0012 (101.7)	0.0024 (23.9)	0.0047 (61.0)

[a] Data represent means (percent CVs) for all parameters except T_{max}, for which data are medians (minima, maxima).
[b] AUC includes 2 doses.

investigator assessed 6 of these events to be not related, 42 events to be possibly related, and 1 event to be definitely related to FV-100. The last event was a headache in a subject in the 400-mg QD group with onset on day 6 and a duration of 1 day. The assessment of the relationship of AEs to FV-100 showed that they were not dose dependent.

FV-100 at 400 mg was also well tolerated when it was administered in single doses and in multiple doses to the elderly subjects in study INH-FV1-004. Physical examination, vital signs, and ECG data from this study were similar to data from the corresponding treatment groups in studies INH-FV1-002 and INH-FV1-003. Laboratory findings were also similar, with the exception of elevated serum glucose in 8 of the 23 subjects who received FV-100 in this study. Serum glucose values measured 24 h after dosing in a fasting state were abnormal (7 cases with grade 1 [110 to 125 mg/dl] and 1 case with grade 2 [126 to 250 mg/dl]) and in most cases remained elevated for several subsequent days, with the values for 3 of the cases rising to grade 2. In 6 of the 8 cases, serum glucose returned to baseline levels by the end of the study. Results of analysis of aggregated data in both the single-dose and multiple-dose cohorts are consistent with these individual results; however, the overall absence of urinalysis findings, specifically, glycosuria, the small number of subjects in this study, and the age group studied do not allow a clear interpretation of these data. The AE data in this study are comparable to the results in the corresponding younger cohorts in studies INH-FV1-002 and INH-FV1-003, and no new toxicities or patterns were observed in this age group. Six (46.2%) subjects who received a single dose of 400 mg FV-100 experienced 7 AEs, none of which were assessed to be definitely related to FV-100 and all of which were mild. The investigators assessed 1 of these events to be not related to FV-100 and 6 events to be possibly related to FV-100. Eight of the 10 elderly subjects who received 7 daily doses of 400 mg FV-100 experienced 10 AEs, none of which were assessed to be definitely related to FV-100. The investigators assessed 8 of these events to be mild, 2 events to be moderate, 6 events to be not related, and 4 events to be possibly related.

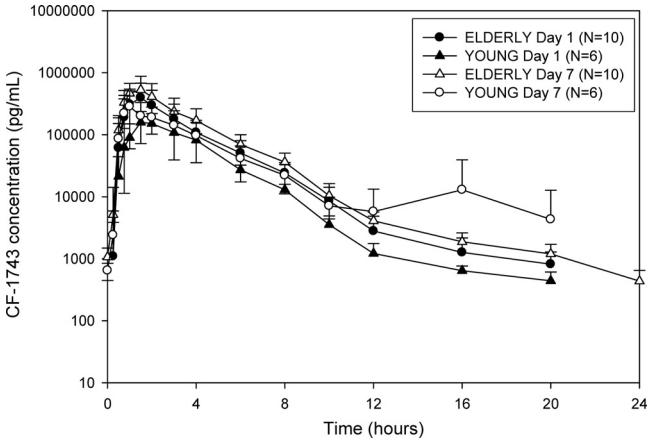

FIG. 5. CF-1743 plasma concentration-time curves following administration of day 1 and day 7 doses of 400 mg FV-100 to healthy young and elderly volunteers (studies INH-FV1-003 and INH-FV1-004).

Table 5 details the AEs reported for 2 or more subjects in any of the studies. The data do not indicate any consistent toxicity for FV-100 or any increased toxicity with increased or repeated doses. It should be noted that for the 2 events coded as infusion site extravasation, the terms recorded by the investigator were "i.v. [intravenous] infiltration" and "intravenous infiltrate." The i.v. referenced was a cannula for blood sample collection; there was no catheter for infusion, and these AEs are not related to study medication administration. It should also be noted that 1 of the subjects for whom neutropenia was recorded was an African-American subject who had low neu-

TABLE 5. Adverse events reported by at least 2 subjects

MedDRA preferred term	No.[a] (%) of subjects												
	FV-100 single doses						FV-100 multiple doses					Total	
			400 mg[b]										
	100 mg (n = 6)	200 mg (n = 6)	Fasted (n = 19)	High-fat meal (n = 6)	Low-fat meal (n = 5)	800 mg (n = 6)	100 mg QD (n = 6)	200 mg QD (n = 12)	400 mg QD (n = 16)	400 mg Q12 h (n = 6)	800 mg QD (n = 6)	FV-100 (n = 83)	Placebo (n = 24)
Headache	1	1	2	3	0	0	3	1	4	0	1	16 (19)	5 (21)
Nausea	0	0	1	1	0	0	0	1	1	1	1	6 (7)	1 (4)
Neutropenia	0	0	2	0	0	0	0	1	1	0	0	4 (5)	0 (0)
Epistaxis	0	0	0	0	1	0	0	0	1	0	1	3 (4)	0 (0)
Somnolence	0	0	1	0	0	0	0	0	1	0	0	2 (2)	1 (4)
Abdominal pain	0	0	0	0	0	0	0	0	0	0	0	0 (0)	2 (8)
Back pain	0	0	0	0	0	0	0	0	1	0	1	2 (2)	0 (0)
Constipation	0	0	1	0	0	0	0	0	0	0	1	2 (2)	0 (0)
Diarrhea	0	0	0	0	0	0	0	1	1	0	0	2 (2)	0 (0)
Dizziness	1	0	0	0	0	0	1	0	0	0	1	2 (2)	0 (0)
Dyspepsia	0	0	0	0	1	0	0	0	0	1	0	2 (2)	0 (0)
Infusion site extravasation[c]	1	0	0	0	0	0	0	0	0	0	1	2 (2)	0 (0)
Pyrexia	0	0	0	2	0	0	0	0	0	0	0	2 (2)	0 (0)
Scleral hyperemia	0	0	0	1	0	1	0	0	0	0	0	2 (2)	0 (0)
Viral infection	0	0	0	0	0	0	0	0	2	0	0	2 (2)	0 (0)
Vomiting	0	0	0	0	0	0	0	0	2	0	0	2 (2)	0 (0)

[a] Number of subjects reporting at least 1 adverse event.
[b] The 6 subjects who received 400 mg FV-100 in the fasted cohort in study INH-FV1-002 were also enrolled in the 400-mg high-fat-meal cohort and 5 were also enrolled in the additional low-fat-meal cohort. The 6 subjects are counted once in the FV-100 total column.
[c] The verbatim terms used by the investigator for these 2 events were "i.v. infiltration" and "intravenous infiltrate." The i.v. referenced is a cannula for blood sample collection; there was no catheter for infusion, and these AEs are not related to study medication administration.

trophil counts prior to dosing and that for the other 3 subjects, although the abnormal neutrophil counts were outside the laboratory normal range, they were transient and did not meet the criteria for grade 1 (mild) toxicity defined in the study protocol. In the 3 studies, there were no AEs leading to study drug discontinuation, no serious AEs, and no deaths.

DISCUSSION

The prodrug FV-100 and its major active metabolite, CF-1743, represent a new class of nucleoside analogues with a novel bicyclic pyrimidine base bearing a long alkyl or *p*-alkylphenyl side chain (9, 10). Their rapid intracellular uptake and strong *in vivo* inhibition of laboratory VZV strains as well as clinical VZV isolates at concentrations in the low nanomolar range may present a novel approach to the unmet clinical challenges in the treatment of HZ and prevention of PHN (1, 9, 10, 11, 12).

Consistent with the results of preclinical investigations, data from the 3 human studies described in this report show that FV-100 is rapidly and extensively converted to CF-1743. Following single and multiple oral doses of FV-100, concentrations of CF-1743 were measurable in plasma within 10 to 30 min of dosing, and CF-1743 comprised >90% of the overall total of measurable metabolites and parent drug in the plasma. The half-life of CF-1743 was independent of dose and ranged from 3.1 to 4.5 h. Although the half-life in plasma was relatively short, CF-1743 concentrations were above the EC_{50} of 170 pg/ml for the entire 24-hour dosing interval for all dose cohorts, suggesting that once-daily dosing of FV-100 will produce adequate concentrations of CF-1743 for efficacy against HZ. Furthermore, the pharmacokinetics suggest that CF-1743 may be widely distributed to peripheral tissues.

The urinary excretion of FV-100 and CF-1743 was low for all dose cohorts following single dosing, under fed and fasted conditions, and following multiple FV-100 dosing, indicating that renal elimination is not a major pathway of elimination for either compound. These data suggest that dosing adjustments will likely not be necessary in patients with altered renal function, since <0.001% of FV-100 and CF-1743 is eliminated in the urine.

A high-fat meal significantly decreased FV-100 and CF-1743 C_{max}s (56% and 87%, respectively) and resulted in significant variability in C_{max} and AUC among individuals receiving FV-100 under fed conditions. The CF-1743 AUC was reduced by 82% following concomitant administration of FV-100 with a high-fat meal. Administration with a low-fat meal did not have an impact on the pharmacokinetics of FV-100 or CF-1743. The observed food effect following a high-fat meal may be attributed to a complex interaction between the physical-chemical characteristics of the compound, including solubility, permeation, and transporter effects, and the postprandial changes in the gastrointestinal environment. On the basis of the results of this study, administration of FV-100 with a high-fat meal is not recommended. Rather, FV-100 should be administered either in the fasted state or with a low-fat meal; this flexibility in FV-100 administration along with the once-a-day dosing regimen should be convenient for patients and enhance compliance.

The FV-100 and CF-1743 PK parameters for subjects aged 65 years and older were comparable to those observed in younger healthy adult subjects receiving the same dose and

dose regimen. In addition, CF-1743 concentrations remained above the antiviral EC_{50} of 170 pg/ml for the entire 24-hour dosing interval in the elderly subjects. These results suggest that FV-100 can be administered without regard to age; dosing modifications will not be required for elderly patients.

Seven days of dosing with FV-100 at doses of 100 to 800 mg daily and 400 mg every 12 h was well tolerated by young adult subjects, and FV-100 at 400 mg daily was well tolerated by elderly subjects. Physical examination, ECG, vital signs, and AE data indicated no consistent toxicity for FV-100. No relationship of AEs to dose and no new toxicities were observed in the elderly population, but there was a higher frequency of AEs in elderly subjects than in the younger group. Among the 83 subjects who received active FV-100 in these 3 studies, the investigators assessed only 1 event to be definitely related to FV-100: a headache in a subject in the young 400-mg QD group. Laboratory data suggested a potential relationship between FV-100 and increased serum glucose in the elderly group, albeit with negative glycosuria, but a definitive interpretation of these data from study INH-FV1-004 is not possible. The significance of this relationship will be assessed in future clinical trials.

In conclusion, the PK and safety profiles of FV-100 in young adult and elderly subjects support the continued investigation of FV-100 for the treatment of HZ and reduction of PHN with once-daily dosing and without dose modifications for elderly or renally impaired patients. A phase II clinical trial evaluating the efficacy and safety of 200 and 400 mg of FV-100 administered daily for 7 days to subjects aged 50 years and over is being conducted.

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