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A Study of the Safety and Pharmacokinetics of Multiple Ascending Doses 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. *In vitro* studies demonstrated that CF-1743 rapidly enters varicella zoster infected cells and can stop viral replication within five minutes of exposure. This study assessed the safety and PK of multiple doses of FV-100 healthy subjects aged 18–55 years. **Methods**: Subjects were randomized into sequential ascending dose cohorts: 100, 200, 400 and 800 mg once daily for 7 days, and 400 mg twice daily for 7 days. In each cohort, 6 subjects received FV-100 and 2 received placebo in a blinded manner. Plasma and urine were collected on Days 1 and 7, and for 96 h following the last dose. Subjects were followed for 14 days after dosing for safety (adverse events, physical exams, ECGs, and clinical labs). Safety data from each cohort were reviewed when subjects completed the Study Day 22 evaluation, and advancement to the next dose level occurred after pre-determined safety criteria were met. **Results**: There were no clinically significant findings for AEs, PEs, ECGs, and clinical laboratory tests. Plasma and urine PK from all cohorts will be presented. Plasma PK parameters (mean, S.D.) for CF-1743 for the 100 and 200 mg cohorts are shown below:

	100 mg		200 mg	
	D1	D7	D1	D7
$T_{1/2}$ (h)	3.7 (0.9)	4.5 (1.8)	3.8 (2.0)	2.6 (1.3)
T_{max} (h)	1.9 (0.2)	2.1 (0.7)	1.8 (0.7)	2.7 (0.8)
C_{max} (pg/mL)	59,167 (40,718)	38,606 (28,234)	93,453 (43,892)	80,656 (85,819)
AUC_{last} (pg h/mL)	171,093 (114,061)	106,185 (72,688)	189,167 (55,216)	203,374 (198,269)
AUC_{INF} (pg h/mL)	201,288 (100,591)	108,052 (73,094)	190,806 (54,911)	242,140 (243,494)

Conclusions: FV-100 was generally well tolerated at the dose levels studied. The PK of CF-1743 increased with increasing dose. The single and repeat dose PK for CF-1743 was comparable. There was no accumulation of CF-1743 upon repeat dose administration.

doi:10.1016/j.antiviral.2009.02.110

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A Study of the Safety and Pharmacokinetics of Single and Multiple Doses of FV-100 in Subjects 65 Years and Over

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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. *In vitro* studies demonstrated that CF-1743 rapidly enters varicella zoster infected cells and can stop viral replication within 5 min of exposure. This study assessed the safety and PK of a single oral dose and multiple doses of FV-100 in subjects ≥65 years. The goal of the study was to compare the safety and PK of FV-100 in elderly subjects to that of subjects ages 18–55 studied previously. **Methods**: Subjects were randomized into 2 dose cohorts: (1) a single dose of 400 mg FV-100, or (2) 400 mg FV-100 once daily for 7 days. In each cohort, 10 subjects received FV-100 and 2 received placebo in a blinded manner. Subjects were followed for 14 days after dosing for safety (adverse events, physical exams, ECGs and clinical labs). Plasma and urine were collected for PK analysis. Safety data from the first cohort were reviewed when subjects completed Study Day 15, and advancement to the second cohort occurred after pre-determined safety criteria were met. **Results**: Study results are forthcoming. Complete safety and PK data will be presented for both cohorts. Comparisons will be made to subjects aged 18–55 studied previously.

doi:10.1016/j.antiviral.2009.02.111

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Study of Anti-Epstein–Barr virus activity of novel fluorinated heterocyclic nucleoside analogues

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Although a number of the licensed antiviral drugs can inhibit EBV replication, none of them has been licensed for the treatment of EBV infection in the clinic [1]. Therefore, search of new effective preparations capable to inhibit herpesviruses reproduction is stipulated by their certain resistance to different groups of chemical preparations. Synthesis of nucleoside analogues with triazole substituents which could be used as pharmaceuticals are of great interest [2]. We have prepared new fluorinated 1,2,3-triazole derivatives (1–3) (Fig. 1) and studied their antiEBV activity. The objective of the present investigation was to study the activity triazole substituents against EBV—lymphotropic and oncogenic virus. As a model of EBV-infection in vitro we used the line of lymphoblastoid B-cells Raji. The first stage of investigation of substances was the analysis of their cytotoxicity for cell line Raji. We have studied in concentrations of 1000–1 μg/ml. In 48 h was conducted the MTT-analysis of the investigated samples. The concentrations which inhibited the quantity of alive cells on 50% (ID_{50}) were equal to substances No. 1—600 μg/ml, No. 2–255 μg/ml and No. 3–800 μg/ml. An inhibition of reproduction of EBV in a cell culture was determined by reduction of a accumulation of the virus capsid antigen proteins on a cell. The anti-virus activity was determined by a cellular ELISA method, using Mab to VCA EBV (AbD Serotec, GB). Drugs were investigated in concentrations of 100–0.1 μg/ml. The analysis of obtained data allowed to determine concentrations, which oppressed the accumulation of the virus proteins on 50%. ED_{50} for No. 1 and No. 3–10 μg/ml, No. 2–50 μg/ml. Thus, proceeding from the index of selectivity for the compound No. 1–60, No. 3–80, it is possible to make a conclusion about their availability for the further researches as of drugs that are active against an EBV.

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doi:10.1016/j.antiviral.2009.02.112