Original article

Unexpected finding of delayed-onset seizures in HIV-positive, treatment-experienced subjects in the Phase IIb evaluation of fosdevirine (GSK2248761)

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Background: Fosdevirine (GSK2248761) is a non-nucleoside reverse transcriptase inhibitor with HIV-1 activity against common efavirenz-resistant strains. Two partially blind, randomized, Phase IIb studies were initiated (1 in treatment-naive and 1 in treatment-experienced subjects with HIV) to select a once-daily dose of fosdevirine for Phase III trials.
Methods: In the SIGNET study, treatment-naive subjects were randomized 1:1:1 to receive once-daily fosdevirine 100 or 200 mg or efavirenz 600 mg, each along with tenofovir disoproxil fumarate/emtricitabine 300 mg/200 mg or abacavir/lamivudine 600 mg/300 mg. In the SONNET study, treatment-experienced subjects with non-nucleoside reverse transcriptase inhibitor-resistant HIV-1 were randomized 1:1:1 to treatment with fosdevirine 100 or 200 mg once daily or etravirine 200 mg twice daily, each along with twice-daily darunavir/ritonavir 600/100 mg and raltegravir 400 mg. The primary efficacy end point was the proportion of subjects with HIV-1 RNA<50 copies/ml. Safety and pharmacokinetics were also addressed.
Results: A total of 35 subjects were exposed to fosdevirine 100 or 200 mg. Trials were halted when 5 treatment-experienced subjects (1 receiving fosdevirine 100 mg, 4 receiving fosdevirine 200 mg) developed new-onset seizures after ≥4 weeks of exposure to fosdevirine. There was no clear association between seizures and fosdevirine plasma drug levels. Time to seizure onset ranged from 28 to 81 days, and all 5 subjects experienced ≥1 seizure after drug discontinuation.
Conclusions: The delayed onset of seizures after fosdevirine exposure and persistence after discontinuation is without precedent in antiretroviral drug development, leading to additional investigation and underscoring the need for careful subject monitoring.

Introduction

Fosdevirine (FDV; GSK2248761, formerly IDX899) is a potent, selective, non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1 replication with low nanomolar activity *in vitro*. Fosdevirine shows good activity against a broad range of HIV-1 strains, including efavirenz (EFV)-resistant clinical isolates [1]. In an early clinical study of healthy subjects, FDV at single doses up to 1,200 mg or multiple doses up to 800 mg for 7 days was well tolerated [2]. A series of subsequent Phase I drug interaction studies up to 21 days in duration failed to reveal any treatment-emergent toxicities in HIV-1 seronegative adults [3]. In a 7-day Phase I/IIa study, FDV monotherapy demonstrated short-term safety and efficacy at doses of 100 to 800 mg in treatment-naive subjects with HIV-1 [4]. Prior to Phase IIb, 187 human subjects had received up to 1,200 mg of FDV for 21 days or less without treatment-emergent serious adverse events (AEs), grade 3 or 4 drug-related AEs, or any AE trend compared with placebo.

Preclinical toxicity studies, *in vitro* and in animals, had not identified an adverse risk of FDV-related central nervous system (CNS) effects prior to initiation of Phase IIB. In addition, there were no CNS effects in a rat neurobehavioral study or in the repeat-dose mouse toxicity studies ≤6 months in duration. However, the maximum feasible exposures were low relative to those needed for clinical efficacy. Pivotal enabling studies included repeat-dose toxicity studies in monkeys from

2 weeks to 9 months achieving FDV systemic exposures approximately 1–6-fold the clinical exposure with no evidence of neurobehavioral signs or CNS histopathological abnormalities, and a quantitative whole-body autoradiography study in mice suggesting minimal brain penetration (unpublished data). The achievable exposures in chronic preclinical toxicity studies were limited by the solubility of FDV and inherent clearance properties. Multiple avenues were pursued to maximize FDV exposure in preclinical models. The *in vitro* binding of FDV (5 μM) to rat, dog, monkey and human plasma was high (>99.3%), which would predict limited CNS penetration.

Given the predicted efficacy and safety of FDV at a range of doses up to 1,200 mg and the demonstrated antiviral activity down to 100 mg in the 7-day monotherapy study, doses of 100 and 200 mg were chosen for further evaluation in two Phase IIb studies: an antiretroviral therapy (ART)-experienced cohort with NNRTI resistance and a treatment-naive cohort.

Methods

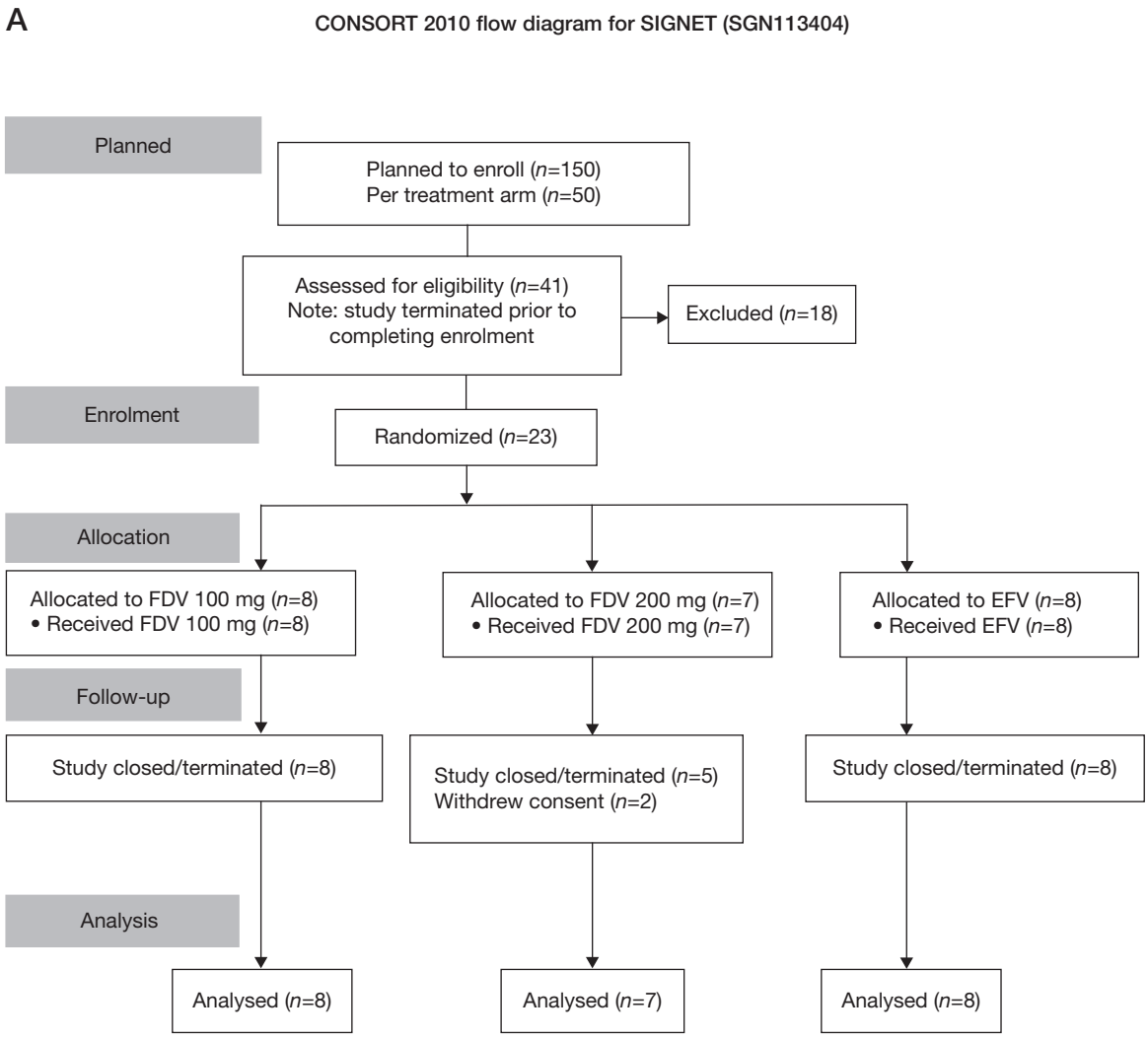
Two randomized, partially blinded, multicentre, parallel group, Phase IIb, dose-finding studies were conducted in adults with HIV-1 to select the optimal dose of FDV (100 or 200 mg once daily). Subjects, investigators and the study team were blinded to the centrally randomized dose of FDV, while the comparator in both studies was administered open label. Both trials were conducted according to the protocols and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements. Written informed consent was obtained from all subjects before treatment, and the protocols were approved by institutional review boards/ethics committees. In the SIGNET study (NCT01231555; ClinicalTrials.gov), HIV-1 treatment-naive subjects with a $CD4^+$ count >200 cells/mm^3 were randomized 1:1:1 to receive FDV 100 mg once daily, FDV 200 mg once daily, or EFV 600 mg once daily, each in combination with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) 300 mg/200 mg or abacavir/lamivudine (ABC/3TC) 600 mg/300 mg (Figure 1A). Randomization was stratified by HIV-1 viral load (VL) at screening (<100,000 or ≥100,000 copies/ml) and choice of backbone therapy (TDF/FTC or ABC/3TC). The SIGNET study randomized subjects in France and Germany.

In the SONNET study (NCT01199731; ClinicalTrials.gov), HIV-1 treatment-experienced subjects with a $CD4^+$ count >100 cells/mm^3 and pre-existing NNRTI genotypic resistance were randomized 1:1:1 to FDV 100 mg once daily, FDV 200 mg once daily, or etravirine (ETR) 200 mg twice daily (Figure 1B). All subjects also received darunavir/ritonavir (DRV/r), 600 mg/100 mg twice daily, and raltegravir (RAL) 400 mg twice daily. Randomization was stratified by HIV-1 VL at screening (<50,000 or ≥50,000 copies/ml) and DRV susceptibility (screening phenotype fold change <7 or ≥7–20). In both studies, the dose of FDV was blinded and the comparator agent was given open label. The SONNET study randomized subjects in Romania and the United States.

The primary efficacy end point for both studies was the proportion of subjects with HIV-1 RNA <50 copies/ml through week 16; secondary end points included safety and pharmacokinetic (PK) assessments. Because these two studies were prematurely discontinued (thereby limiting the number of subjects randomized and the duration of exposure), an observed analysis was used to summarize efficacy and no comparisons by treatment arm were performed. Additional unplanned analyses were conducted to explore relationships between potential risk factors and on-treatment observations and seizures. The variables explored included treatment (group, FDV versus control, FDV dose levels), age, sex, ethnicity, country, $CD4^+$ count, FDV exposure levels, HIV-1 RNA level, and serum chemistry and haematology values at baseline and over time. Three different types of models were explored: logistic regression models, Cox proportional hazards models that accounted for time to the event, and Poisson regression models that adjusted for exposure time and dose level. Because of the small number of events, only univariate models were fit, except for the Poisson regression models that controlled for FDV dose level and each of the other factors one at a time. These models were run using the data from SONNET alone and also using pooled data from the SONNET and SIGNET studies. In addition, the time to seizures, switch, withdrawal, or last contact were explored graphically by treatment group for each study (Figure 2A and 2B).

Plasma FDV, DRV and ritonavir PK parameters were determined by non-compartmental analysis of individual plasma concentration time data using WinNonlin version 5.1 or higher (Pharsight Corporation, Mountain View, CA, USA). Actual elapsed time from dosing was used to estimate all individual plasma PK parameters for evaluable subjects. Values for maximum observed plasma concentration (C_{max}), time of occurrence of C_{max} (T_{max}), terminal elimination phase half-life and area under the concentration–time curve ($AUC_{0\text{-}t}$) were estimated following administration of FDV at weeks 2, 8 and 24 (when available). Week 2 intensive or sparse PK samples were collected from 8 subjects in the SIGNET study and from 6 subjects in the SONNET study, evenly split between 100 and 200 mg. Post-week 2 PK samples were available from 9 additional subjects in the SONNET study.

Figure 1. CONSORT flow diagrams for the SIGNET and SONNET studies



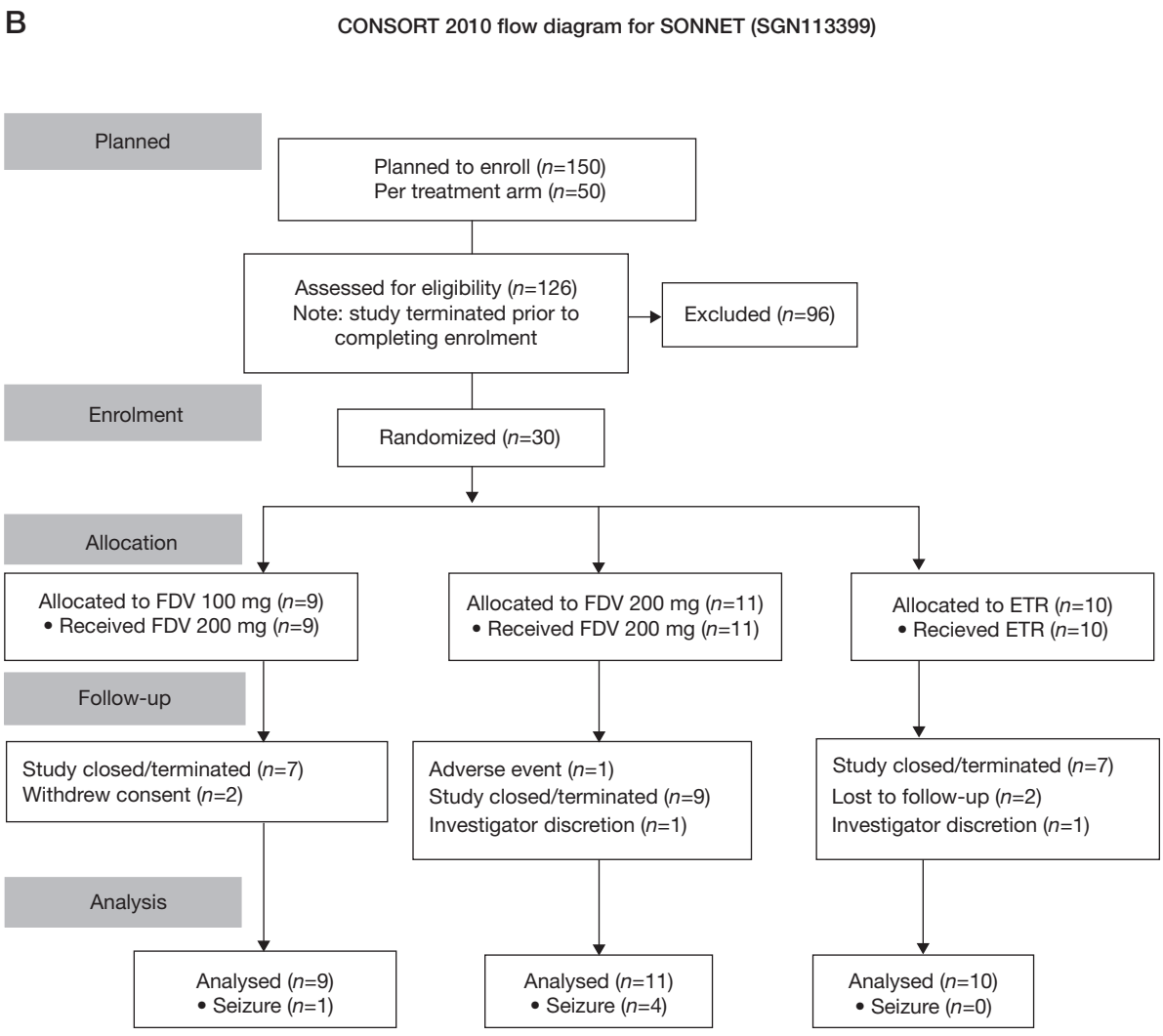
CONSORT flow diagrams for the **(A)** SIGNET and **(B)** SONNET studies. EFV, efavirenz; ETR, etravirine; FDV, fosdevirine.

Results

A total of 53 subjects were randomized to treatment in the 2 studies (23 treatment-naive and 30 treatment-experienced subjects) between 9 October 2010 and 19 July 2012 (SONNET), and between 18 November 2010 and 4 July 2012 (SIGNET). The majority of subjects were male (81%) and White (68%). In the SIGNET study, 87% of subjects had a baseline VL of <100,000 copies/ml at enrolment, and 57% of subjects had a CD4$^+$ count >350 cells/mm^3 (median of 397 cells/mm^3). In the SONNET study, nearly two-thirds (63%) of the population had a VL of <50,000 copies/ml and a CD4$^+$ cell count <200 cells/mm^3 (median of 141 cells/mm^3).

Between both trials, 35 patients received ≥1 dose of FDV, 15 in SIGNET and 20 in SONNET. Combined, 17 and 18 subjects received 100 and 200 mg of FDV, respectively. Exposure to FDV was relatively short and varied from 7 to 56 days in treatment-naive subjects (mean duration of FDV exposure of 23.6 days) and from 6 to 81 days in treatment-experienced subjects (mean duration of FDV exposure of 44 days). In SONNET and SIGNET, 13 of 20 subjects (65%) and 6 of 15 subjects (40%), respectively, had ≥4 weeks of FDV exposure. Although antiviral activity was observed in patients in the intent-to-treat exposed population, the short time on randomized FDV limited the ability to evaluate the standard HIV efficacy parameters for FDV.

Figure 1. Continued



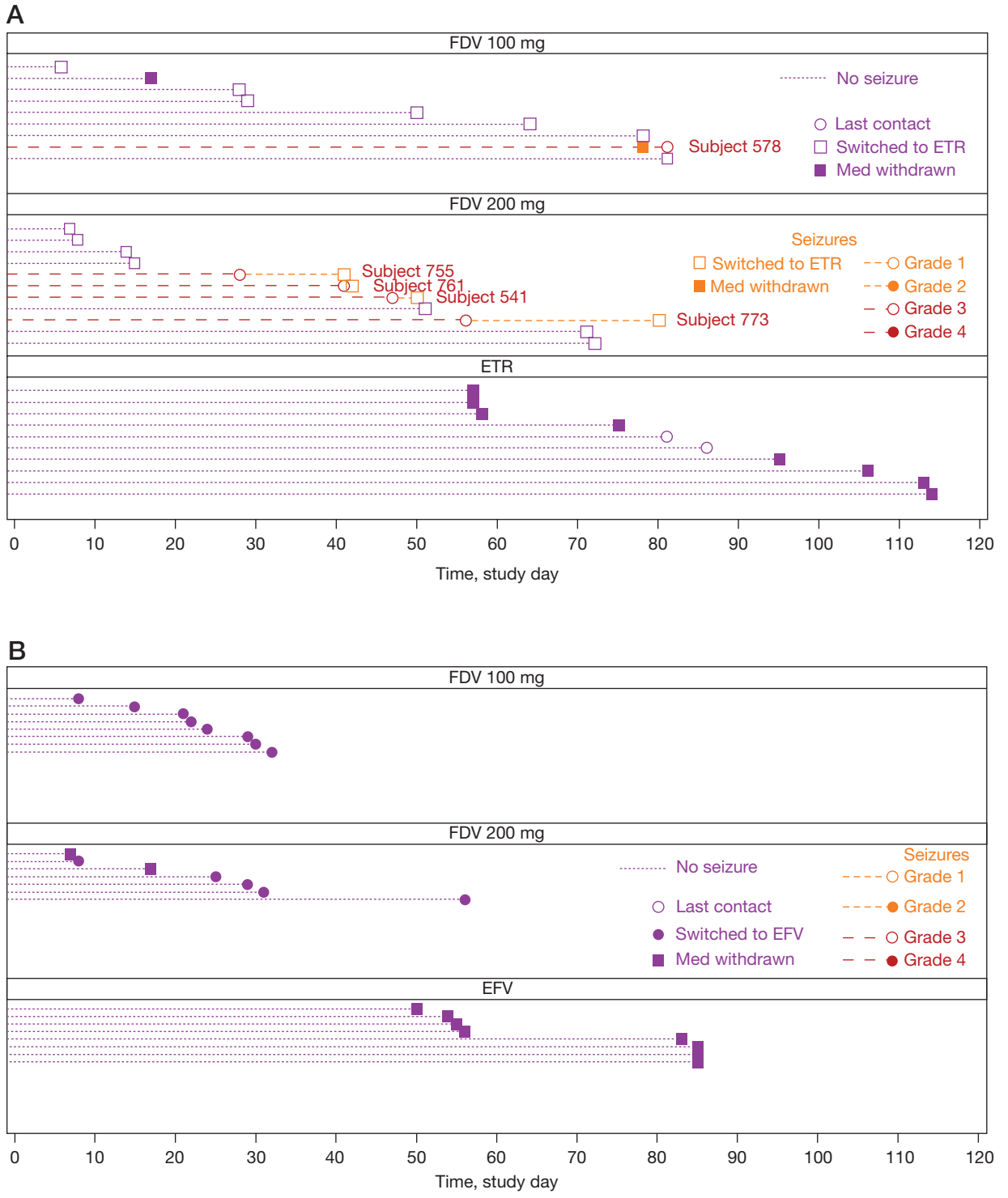
FDV was absorbed rapidly following oral dose administration, with a median time to maximum concentration of approximately 4 h in most subjects at either dose with exposures consistent with earlier predictive data [4]. There was a moderate to high degree of variability observed for most of the key PK parameters.

Safety

The most commonly reported clinical AEs in treatment-naive subjects (SIGNET study) while receiving FDV were somnolence (*n*=2; 13%) and nightmares (*n*=2; 13%). There were two serious AEs unrelated to FDV: rash and colitis. The most commonly reported clinical AEs in treatment-experienced subjects (SONNET study) while receiving FDV included seizure (*n*=4; 20%), diarrhoea (*n*=4; 20%), pruritus (*n*=2; 10%) and sinusitis (*n*=2; 10%). One additional subject in SONNET, randomized to FDV, had an initial seizure 3 days after FDV treatment withdrawal, constituting 5 total subjects experiencing seizures.

A total of 5 treatment-experienced subjects reported seizures after being exposed to FDV (1 receiving FDV 100 mg and 4 receiving FDV 200 mg), while none of the subjects in the ETR arm reported a seizure. No seizures were reported in treatment-naive subjects. Time to onset of first seizure ranged from 28 to 81 days; all 5 subjects who experienced a seizure had received FDV for ≥4 weeks (Figure 2). All 5 subjects developed recurrent seizures ranging from 1 week to 5 months after drug discontinuation. All initial seizures were described as tonic–clonic in nature, whereas subsequent seizures were described as tonic–clonic, partial or atypical.

Figure 2. Time to first seizure, switch, discontinuation or last contact for treatment-experienced subjects enrolled in the SONNET and SIGNET studies



Time to first seizure, switch, discontinuation or last contact for treatment-experienced subjects enrolled in the **(A)** SONNET and **(B)** SIGNET studies. In this figure, the dotted line indicates the length of time on study for subjects without seizure, through to their last contact (open circle) or change to the comparator regimen (closed circle for efavirenz [EFV] and open square for etravirine [ETR]). Subjects with a hashed line to a circle indicate subjects who had a seizure, with the circle indicating the time of the subject's first seizure while on study. Seizure subjects either discontinued drug (closed squares) or switched to ETR (open squares). The time of switch is based on when the subject stopped taking fosdevirine (FDV) before switch.

Two subjects were found to have pre-existing abnormal brain anatomy of unknown significance: right cerebral volume loss and agenesis of the corpus callosum. One subject developed haemorrhagic encephalitis concurrent with the onset of seizures that may have been related to immune reconstitution inflammatory syndrome or undiagnosed viral infection. With the exception of the subject with encephalitis, computed tomography (CT) and magnetic resonance imaging (MRI) of the brain were negative for acute pathology in all subjects. No potentially epileptogenic concomitant medications were in common across the subjects. None of the subjects had a prior history of seizure or epilepsy, although one subject had a family history of seizures in his mother. Case vignettes are provided as supplementary material (Additional file 1).

As a result of the unexpected finding of seizures, all clinical development with FDV was placed on hold, and all subjects who had been on FDV were required to either switch to the respective comparator or withdraw from the trial. All seizures were medically managed in consultation with neurologists, and subjects were provided with antiepileptogenic medications. Subjects were followed for a minimum of 8 weeks after withdrawal from the Phase IIb study, and subjects with seizures were followed for a minimum of 12 weeks after study withdrawal. A drug-exposure registry was subsequently created to follow SIGNET and SONNET study subjects who experienced seizures for a minimum of 2 years after the last dose of FDV and to follow subjects who did not experience seizures for 1 year after FDV discontinuation. No additional seizures have been reported since completion of the follow-up period within the Phase IIb studies.

Pharmacokinetics

The concentrations of FDV in plasma were in-line with those predicted based on previous clinical trials where repeat daily doses of up to 800 mg or single doses of up to 1,200 mg had been administered with no signs of safety issues or lack of tolerability. C_{min}/IC_{50} ratios (calculated at week 2) were around 25. Selected median PK parameters for FDV in treatment-experienced patients are summarized in Table 1. The overall PK profile of subjects experiencing a seizure was not different than that for subjects who did not experience seizures, and there were no discernible relationships between FDV exposure (any given PK parameter) and seizures in any subject experiencing seizures. Plasma FDV concentration in subjects who experienced seizures were encompassed by FDV concentrations in subjects who did not experience seizures (Figure 3).

Exploratory analyses examined potential factors associated with seizures (Tables 2 and 3). Poisson regression models accounting for exposure time and controlling for FDV dose level as a covariate while exploring all the other factors univariately indicated that the following factors were found to increase the likelihood of a seizure: higher FDV dose level, higher week 2 change from baseline in white blood cell count, and higher week 2 change from baseline in neutrophils. Similar results were seen in the logistic regression models and Cox proportional hazards models with the addition of higher baseline total bilirubin as a significant factor in both models and lower week 4 change from baseline in total bilirubin in the Cox proportional hazard model. The absolute difference between the groups with regard to total bilirubin, white blood cell counts and neutrophil counts was not clinically significant. Similar results were obtained when data from both trial populations were pooled with the addition of age as a significant factor based on the logistic regression model only.

Discussion

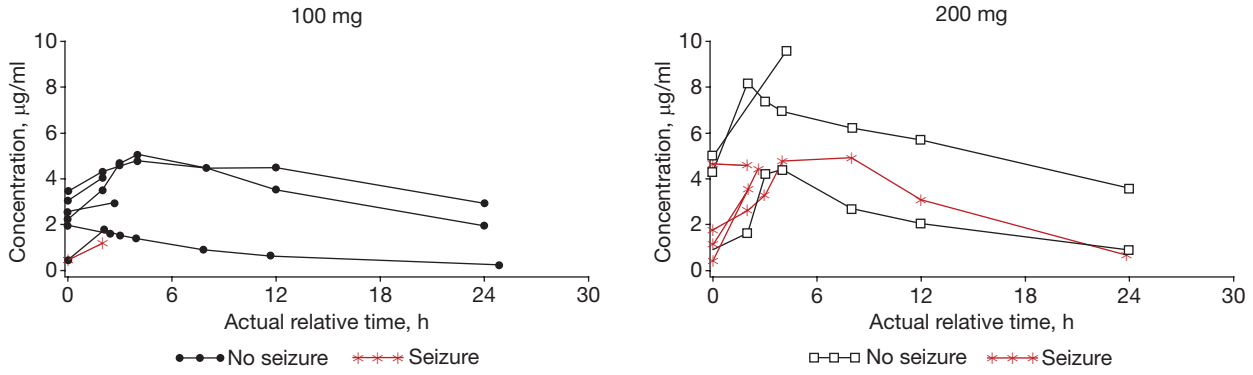
The estimated prevalence rate for epilepsy in the general population based on US and European population-based studies is between 0.3% and 1.0% [5–13], and a meta-analysis of epilepsy incidence studies determined a median incidence of 0.047% [14]. However, several studies have shown that the incidence of new-onset seizures can be higher in patients with HIV and may range from 3.1% to 11.1% [15–17]. In many cases, the seizures were not associated with any identifiable cause and were potentially associated with HIV infection alone [15,18].

Table 1. Selected week 2 FDV median pharmacokinetic parameters

		Parameter (range)				
FDV dose, mg	*n*	C_{max}, µg/ml	$AUC_{0-\tau}$, µg•h/ml	C_{τ}, µg/ml	T_{max}, h	$t_{1/2}$, h
100	3	4.81 (1.8–5.0)	82.63 (18.3–98.0)	1.97 (0.3–2.9)	4.0 (2.1–4.0)	13.74 (9.1–27.7)
200	3	4.92 (4.4–8.2)	69.26 (51.2–133.5)	0.88 (0.7–3.6)	4.0 (2.0–8.0)	9.90 (5.6–20.8)

AUC, area under the concentration–time curve; C_{max}, maximum observed plasma concentration; C_{τ}, concentration at the end of dosing interval; FDV, fosdevirine; $t_{1/2}$, terminal elimination phase half-life; T_{max}, time of occurrence of C_{max}.

Figure 3. Individual fosdevirine plasma concentrations over time for subjects who did not experience and who did experience seizures at fosdevirine 100 mg and 200 mg doses



Seizure in patients with HIV may also be caused by ART. Indeed, seizure/convulsion is listed as an AE associated with several ARTs across multiple drug classes. For example, seizure/convulsion has been reported in patients receiving the protease inhibitors ritonavir [19], nelfinavir [20] and saquinavir [21], the chemokine receptor 5 antagonist maraviroc [22], and the nucleoside reverse transcriptase inhibitor zidovudine [23]. Seizures have been described as an AE associated with both of the NNRTIs used in these studies, EFV and ETR [24,25]. However, despite the association noted between ART use and seizures, rates of seizures during clinical trials with ARTs have generally been in-line with population estimates and true drug-relatedness is often clouded by comorbidities and underlying conditions in affected subjects.

Table 2. Predictors for seizure based on data from SGN113399

Strata	Seizure rate
Treatment group	
Etravirine 200 mg twice daily	0/10 (0%)
FDV 100 mg once daily	1/9 (11%)
FDV 200 mg once daily	4/11 (36%)
Sex	
Female	1/9 (11%)
Male	4/21 (19%)
Ethnicity	
White	3/14 (21%)
Other	2/15 (13%)
Country	
United States	5/29 (17%)
Other	0/1 (0%)
Exposure ≥20 days	
Yes	5/24 (21%)
No	0/6 (0%)

Data are *n*/total *n* (%). FDV, fosdevirine.

The unexpected finding of seizures in treatment-experienced subjects receiving FDV led to an immediate halt to all clinical studies and an investigation into the possible epileptogenic effect of FDV. No seizures occurred before 4 weeks of FDV exposure, suggesting a delayed onset of effect. Although there was a disproportionate number of seizure subjects on the higher FDV dose, PK/exposure data did not suggest that higher plasma exposures were associated with onset of seizures. The other factors found to be statistically significant were small changes from baseline at week 2 in white blood cell and neutrophil counts, which were not considered clinically meaningful. Given the small number of subjects, the relatively short duration of treatment for most subjects, and the limited number of samples available for analysis, it is difficult to establish whether there may have been unifying risk factors in the subjects who had seizures, which may have elevated their risk of having a seizure while on FDV. HIV infection has been noted to increase the permeability of the blood–brain barrier [26,27], perhaps allowing for increased CNS drug penetration. As the permeability of the blood–brain barrier in subjects in either group was not determined and the duration of the treatment-naive study was short, comparisons between the populations are limited.

Post hoc investigations designed to better understand the epileptogenic potential of FDV are more fully described in a separate manuscript [28]. In brief, an analysis conducted on cerebrospinal fluid (CSF) samples obtained by consent from 4 of the 5 seizure subjects 6, 18, 22 or 40 days after discontinuing FDV detected FDV metabolites in the CSF from all 4 subjects. Samples of CSF were not available from subjects who did not report seizures because this was not required as part of

Table 3. Covariate summaries by seizure group (SGN113399)

Parameter	Seizure group (*n*=5)	No seizure group (*n*=25)
Age, years	46 (40, 60)	43 (22, 59)
Minimum $CD4^+$ count, cells/mm^3	213 (39, 373)	130 (19, 436)
FDV exposure until convulsion/stopping study drug, days	47 (28, 81)	58 (6, 114)
Log RNA, copies/ml		
Baseline = day 1 (*n*=5, 25)	4.51 (3.1, 5.1)	4.53 (1.6, 5.8)
Week 2 change from baseline (*n*=5, 22)	-2.36 (-2.6, -1.5)	-2.05 (-3.1, 0.0)
Week 4 change from baseline (*n*=4, 15)	-2.76 (-2.9, -1.5)	-2.25 (-3.7, 0.0)
Total bilirubin, mmol/l		
Baseline = day 1 (*n*=5, 25)	8 (6, 40)	6 (4, 20)
Week 2 change from baseline (*n*=5, 21)	-2 (-32, 8)	0 (-4, 12)
Week 4 change from baseline (*n*=4, 16)	-6 (-30, 4)	0 (-10, 0)
White blood cell count, GI/l		
Baseline = day 1 (*n*=5, 25)	4.2 (2.3, 8.0)	4.3 (2.1, 6.7)
Week 2 change from baseline (*n*=5, 21)	1.3 (0.5, 4.4)	0.3 (-2.5, 2.4)
Week 4 change from baseline (*n*=4, 16)	1.6 (-2.0, 4.0)	0.45 (-1.6, 3.9)
Neutrophils, GI/l		
Baseline = day 1 (*n*=5, 25)	1.81 (1.27, 6.15)	2.34 (1.08, 4.64)
Week 2 change from baseline (*n*=5, 21)	1.09 (0.09, 3.40)	-0.07 (-2.58, 2.05)
Week 4 change from baseline (*n*=4, 16)	1.62 (-1.84, 2.66)	0.20 (-1.73, 2.17)

Data are median (minimum, maximum). FDV, fosdevirine.

the original study design. Detection of drug metabolites in the CSF after discontinuation of FDV was not predicted by the plasma half-life of FDV (approximately 9–13 h) and is an intriguing result. Because the epileptogenic potential of the identified metabolites was not evaluated and CSF samples from subjects who did not experience seizures were not obtained, the finding can only be considered an association.

A study in minipigs was being conducted during the Phase IIb programme to identify a second non-rodent species in which it was possible to increase systemic exposures of FDV. One minipig that received escalating doses of FDV (100, 500 and 1,000 mg/kg) exhibited neurobehavioral signs within 2–4 h after each dose that resolved by 24 h. Three additional animals exhibited neurobehavioral signs 8–25 days after the last dose of 1,000 mg/kg. No seizures were witnessed. The animals were processed for histopathological examination and no CNS abnormalities were found. An additional post hoc analysis of the CNS disposition and metabolism of FDV that examined samples from rabbit, minipig and monkey studies is reported elsewhere [28].

An additional post hoc analysis demonstrated that FDV (parent molecule) inhibited g-aminobutyric acid a (GABAa) with an IC_{50} of 0.6 µM (positive control picrotoxin IC_{50} of 0.3 µM) *in vitro*, raising the possibility of an off-target pharmacological effect of FDV [28]. Fosdevirine metabolites were not evaluated for GABA inhibition. The inhibition of GABAa provides a possible link between FDV and seizures.

The available data suggest that the development of seizures in treatment-experienced subjects with HIV receiving FDV in combination with DRV/r and RAL for ≥4 weeks was likely related to treatment with FDV. In a clinical drug interaction study, plasma FDV AUC_{0-t}, C_{max} and C_t increased 41%, 34% and 58%, respectively, and DRV/r exposures were unchanged when repeat doses of DRV/r 600 mg/100 mg twice daily were coadministered with FDV 100 mg once daily [3]. In addition, FDV levels were not appreciably higher in seizure subjects or the SONNET study compared with the SIGNET study. The delayed onset of seizures and persistence after drug discontinuation may be consistent with either a long-lived CNS epileptogenic metabolite or may suggest the presence of small niduses of white matter tissue damage capable of acting as durable epileptogenic foci. Chronic toxicity studies in primates, at parity to human exposures, failed to detect CNS toxicity, which may suggest a species-dependent mechanism [28]. The potential differences in drug metabolism and cellular transporters between species underlie the importance of cross-species toxicological studies. The high protein binding of FDV did not preclude the detection of drug-related material in CSF after drug discontinuation. The

theoretical role that ritonavir may have played in increasing CNS retention of FDV and/or FDV metabolites through P-glycoprotein inhibition is unknown but presents an additional hypothesis to explain the CNS toxicity observed in this study. Secondary pharmacological screens for off-target receptor binding can provide important data for the conduct and safety monitoring of clinical studies. In the case of FDV, although post hoc analysis provided some clues as to a potential epileptogenic mechanism of FDV, the preclinical dataset did not predict a significant risk for seizures in human subjects. The clinical development of FDV has been terminated.

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Additional files

Additional file 1: Clinical vignettes of subjects with seizures can be found at http://www.intmedpress.com/uploads/documents/2919_Margolis_Addfile.pdf

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