Antiviral activity, pharmacokinetics and safety of vicriviroc, an oral CCR5 antagonist, during 14-day monotherapy in HIV-infected adults

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Objective: To determine antiviral activity, pharmacokinetic properties, and safety of vicriviroc, an orally available CCR5 antagonist, as monotherapy in HIV-infected patients.

Design and methods: An ascending, multiple dose, placebo-controlled study randomized within treatment group. Forty-eight HIV-infected individuals were enrolled sequentially to dose groups of vicriviroc: 10, 25 and 50 mg twice a day, and were randomly assigned within group to receive vicriviroc or placebo (16 total patients/group) for 14 days.

Results: Significant reductions from baseline HIV RNA after 14 days were achieved in all active treatment groups. Suppression of viral RNA persisted 2–3 days beyond the end of treatment. Reductions of 1.0 $\log_{10}$ HIV RNA or greater were achieved in 45, 77 and 82% of patients in the three groups, respectively. Eighteen, 46 and 45% of subjects achieved declines of 1.5 $\log_{10}$ or greater in HIV RNA in the three groups, respectively. Vicriviroc was rapidly absorbed with a half-life of 28–33 h, supporting once-daily dosing. Pharmacokinetic parameters were dose linear; steady state was achieved by day 12. Two subjects experienced a transient detectable X4-tropic virus. Vicriviroc was well tolerated in all dose groups. The frequency of adverse events was similar in the vicriviroc and placebo groups: 72 and 62%, respectively. The most frequently reported adverse events included headache, pharyngitis, nausea and abdominal pain, which were not dose related.

Conclusion: Whereas all doses were well tolerated and produced significant declines in plasma HIV RNA, total oral daily doses of 50 or 100 mg vicriviroc monotherapy for 14 days appeared to provide the most potent antiviral effect in this study.

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Introduction

A growing understanding of the molecular mechanisms involved in HIV entry into host cells has yielded several novel targets for pharmacological intervention. After attachment to the cellular CD4 receptor, HIV binds to a co-receptor, either the CCR5 (R5 viruses) or CXCR4 (X4 viruses) host chemokine co-receptors [1–4].

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Binding to the chemokine co-receptor leads to additional conformational changes in the viral envelope protein, allowing fusion with the cell membrane and entry of the viral core into the host cell [5]. Several agents have proved to provide significant antiviral effects via novel mechanisms by blocking any one of these steps [6–10].

Targeting the CCR5 co-receptor is particularly attractive as patients with high levels of serum CC chemokines maintain more stable CD4 T-cell counts and have slower disease progression [11]. Furthermore, genetic studies indicating that individuals homozygous for the defective CCR5-delta-32 allele (approximately 1% of the Caucasian population) demonstrate natural protection from HIV with little impact on their health [12,13].

Vicriviroc, formerly known as SCH 417690, is a CCR5 receptor antagonist in clinical development. Vicriviroc binds CCR5 with high affinity and selectivity, demonstrates potent antiviral activity in cell-based entry and replication assays [14], and possesses equal in-vitro activity against genotypically diverse HIV isolates harboring single and multiple resistance mutations within the reverse transcriptase, protease, and gp 41 genes [15].

An evaluation of vicriviroc in healthy non-HIV-infected individuals revealed excellent pharmacokinetic properties. The compound was highly orally bioavailable, only approximately 84% of protein bound in human plasma, and exhibited a half-life exceeding 24 h, supporting once-daily dosing. Vicriviroc is metabolized predominantly by CYP3A4, with minor metabolism by CYP3A5 and CYP2C9. Vicriviroc is not an inducer or inhibitor of CYP3A4, nor is it a substrate for p-glycoprotein. Elimination is by both the renal and hepatic routes.

Materials and methods

Study design and patients

This was an ascending multiple-dose, placebo-controlled study randomized within dose level. Patients were recruited from multiple centers in France, Germany, and the Netherlands. Patients eligible to enroll in this study were HIV-1-infected adults (aged 18–55 years) with plasma HIV-RNA levels between 5000 and 200 000 copies/ml, CD4 T-lymphocyte counts of 200 cells/μl or greater, and confirmed R5 virus phenotype. Subjects were either treatment-naive or had not received antiretroviral therapy for at least 8 weeks. Individuals who tested positive for X4 viruses, or for hepatitis B or C infection, were not eligible for enrollment. All subjects gave written informed consent, which was approved by local accredited institutional review boards. The study was conducted in accordance with the Helsinki Declaration.

Forty-eight subjects were to be assigned to treatment with sequentially ascending doses of oral vicriviroc: 10, 25, and 50 mg twice a day. Eligible subjects were randomly assigned in a ratio of three to one to vicriviroc or placebo in a blinded manner (total 16 subjects per dose group). The study progressed to each higher dose level after safety evaluations and a 7-day washout period at the lower dose level. Patients were hospitalized at the study site from days −2 to 7, and days 12–14 for safety, pharmacokinetic, and pharmacodynamic assessments. Outpatient visits were scheduled for days 9, 11, 15, 16, 17, 21, 25, and 28. Patients were dosed twice a day on days 1–13; only the morning dose was given on day 14. Doses were administered 90 min before or at least 90 min after meals, except on days 1 and 14, when subjects underwent an overnight fast until 4 h after the morning dose.

Pharmacokinetic analysis

Blood samples for vicriviroc pharmacokinetic analyses were drawn over the dosing interval on day 1 and up to 7 days after the morning dose on day 14. Vicriviroc plasma levels were determined using validated tandem mass spectrometry with a lower limit of quantification equal to 0.5 ng/ml (Advion Biosciences, Inc., Ithaca, New York, USA). Plasma vicriviroc concentrations were used to determine the maximum concentration (C_{max}), time of maximum concentration (T_{max}), and minimum (trough collected predose) concentration (C_{min}). The area under the plasma concentration-time curve (AUC) from 0 to 12 h after dosing was calculated using the linear trapezoidal method (Pharsight Knowledgebase Server version 2.0.1 with WinNonlin version 4.0.1; Pharsight Corporation, Cary, North Carolina, USA). The AUC and Cmax were used to assess dose proportionality.

Additional pharmacokinetic parameters determined from the multiple-dose data on day 14 included the apparent terminal-phase half-life, apparent total body clearance (Cl/F), and apparent volume of distribution at steady state.

Antiviral activity

Blood samples for the determination of plasma HIV RNA were obtained at screening, baseline, and before the morning dose on days 1–7, 9, 11, 13, and 14, and during the morning hours on days 15, 16, 17, 21, 25, and 28. HIV RNA, as determined by quantitative polymerase chain reaction (Roche COBAS Amplicor HIV-1 monitor test v1.5; Roche Inc., Somerville, New Jersey, USA), with a lower limit of quantification of 50 copies/μl.

Viral tropism and susceptibility

Blood samples for viral tropism phenotype and vicriviroc susceptibility were collected at screening (viral tropism only), baseline, and days 7, 14, and 28. Viral tropism was

determined using the PhenoSense HIV co-receptor tropism assay (Monogram Biosciences, South San Francisco, California, USA). Viral susceptibility to vicriviroc was assessed by determining the IC_{50} and IC_{95} to HIV-1 isolates using an entry inhibitor susceptibility assay (Monogram Biosciences).

Safety analysis

Safety was assessed on the basis of physical examinations, multiple time-matched electrocardiograms, and routine laboratory tests, which were performed periodically throughout the study. Patients were observed continuously during the period of in-hospital confinement for possible adverse events. Investigator(s) assessed the intensity (mild, moderate, severe, or life-threatening) of each adverse event and its possible relationship to the study drug.

Statistical analysis

All plasma concentration data at each sampling time and pharmacokinetic parameters were expressed as a mean and coefficients of variation for each dose level, with the exception of T_{max}, which is reported as the median plus the range. A repeated-measures analysis of variance model with extraction of the effects due to patient, day, and dose was performed on the log-transformed C_{max} and AUC. To assess the steady state, analysis of variance was performed on the morning and evening trough (C_{min}) concentration data for days 12, 13, and 14 using patient and (successive) times as factors. Statistical analysis was conducted using a program based on SAS/STAT (release 6.12; SAS Institute Inc., Cary, North Carolina, USA). Ninety per cent confidence intervals around the mean, based on log-transformed values, were provided for C_{max} and AUC, dose-adjusted C_{max} and $AUC_{0-12\,h}$.

The change from baseline plasma HIV RNA was calculated as the mean change for each dose group at all timepoints tested. Each active dose group was compared with the pooled placebo group using Wilcoxon and stochastic ordering.

Results

Forty-seven of the 49 HIV-infected, randomly assigned patients (40 men, nine women) completed the study. One patient, who was replaced, discontinued for personal reasons before receiving study medication and a second patient (25 mg twice a day) discontinued vicriviroc early because of an adverse event of fever. One patient randomly assigned to receive vicriviroc 50 mg twice a day mistakenly received placebo. Data from this patient were included in the placebo group for analysis.

Demographic and baseline characteristics of the study patients were similar across dose groups with regard to age and weight (Table 1). The mean baseline HIV RNA was also similar across dose groups, and although mean absolute CD4 T-lymphocyte counts were not vastly different, wide variability was observed across the dose groups.

Pharmacokinetic analysis

After oral administration, vicriviroc was rapidly absorbed, achieving C_{max} within 1.0 to 1.5 h post-dose, across all doses studied. The systemic exposure ($AUC_{0-12\,h}$ and C_{max}) of vicriviroc increased linearly across the 10–50 mg twice-daily dose range on day 1 and at steady state (day 14). After reaching peak levels, plasma concentrations of vicriviroc declined slowly with a mean terminal half-life of 28–33 h. The mean plasma vicriviroc concentration-time profiles at each dose level on day 14 are shown in Fig. 1. Pharmacokinetic parameters were determined based on data from 35 subjects on day 1 and 34 subjects on day 14. Pharmacokinetic parameters demonstrated an approximate twofold accumulation of vicriviroc over the

Table 1. Demographic and baseline characteristics of patients.

	Vicriviroc mg/dose twice a day				
Parameter	Placebo ($n=13$)	10 mg ($n=12$)	25 mg ($n=13$)	50 mg ($n=11$)	All subjects ($n=49$)
Age, (years)					
Mean (SD)	38.7 (7.6)	39.0 (7.4)	36.8 (7.6)	37.7 (8.6)	38.0 (7.6)
Sex, *n* (%)					
Female	3 (23)	1 (8)	1 (8)	4 (36)	9 (18)
Male	10 (77)	11 (92)	12 (92)	7 (64)	40 (82)
Race, *n* (%)					
Black	1 (8)	1 (8)	0	1 (9)	3 (6)
Caucasian	12 (92)	11 (92)	12 (92)	8 (73)	43 (88)
Hispanic	0	0	1 (8)	2 (18)	3 (6)
HIV RNA (log_{10})					
Mean (SD)	4.63 (0.46)	4.31 (0.64)	4.44 (0.54)	4.81 (0.49)	4.55 (0.55)
CD4 cell count (cells/μl)					
Mean (SD)	431 (199.1)	600 (217.2)	495 (247.0)	384 (184.0)	ND

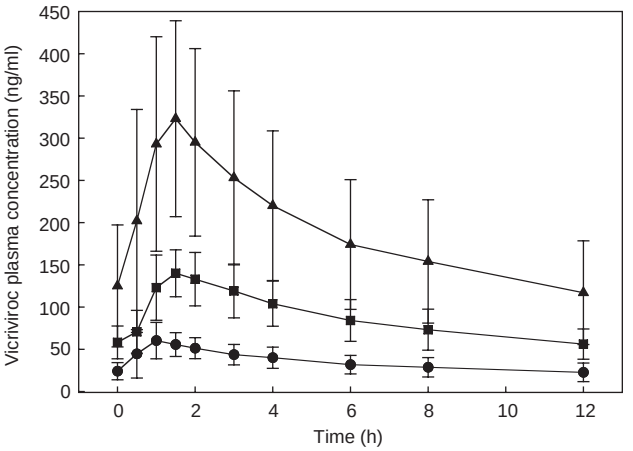

Fig. 1. Mean 12-h plasma vicriviroc concentration versus time profiles after 14 days of oral vicriviroc dosing. —●— 10 mg twice a day ($n = 11$); —■— 25 mg twice a day ($n = 13$); —▲— 50 mg twice a day ($n = 11$).

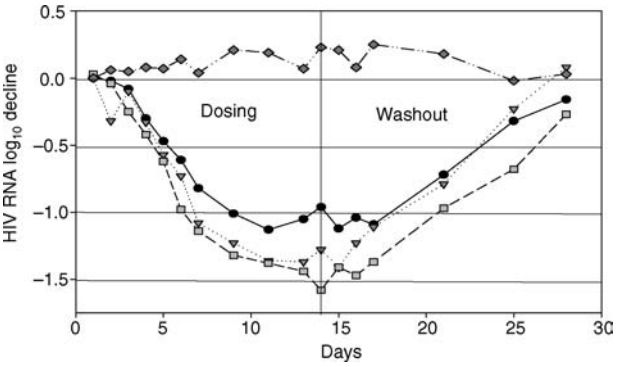

Fig. 2. Mean change from baseline of HIV RNA (log_{10} over 14 days of treatment). –◇– Placebo; —●— vicriviroc 10 mg twice a day; ···▽··· vicriviroc 25 mg twice a day; – –□– – vicriviroc 50 mg twice a day.

14 days of dosing, with steady state being reached by day 12 in all three treatment groups (Table 2).

Over the 10–50 mg dose range, the mean apparent volume of distribution on day 14 was large (range 778–960 l), suggesting extensive distribution into extravascular tissue. Total body clearance of vicriviroc on day 14 was dose independent, with mean Cl/F values of 21–22 l/h observed over the dose range studied.

Antiviral activity

The mean change from baseline HIV RNA over the 14-day dosing period for all three active treatment groups demonstrated the potent antiviral activity of vicriviroc. Significant reductions in HIV RNA relative to placebo were achieved beginning on day 5 for all three vicriviroc doses ($P \leq 0.0001$). Beginning on day 6 there was greater viral suppression in the two higher dose groups compared with the lowest dose group (10 mg twice a day), a difference that reached statistical significance on days 6, 7, and 14 ($P < 0.05$) for the 50 mg twice-daily group, and on days 7 and 14 in the 25 mg twice-daily group ($P < 0.05$; Fig. 2). By day 14 of vicriviroc dosing, the mean viral suppression achieved was -0.93 ± 0.7, -1.49 ± 0.7, and -1.62 ± 0.7 log_{10} for the 10, 25 and 50 mg twice-daily groups, respectively ($P \leq 0.0001$ for each dose versus placebo). Five out of 11 (45%), 10 out of 13 (77%), and nine out of 11 (82%) subjects achieved a decline greater than 1.0 log_{10} in HIV RNA by day 14 in the 10, 25, and 50 mg twice-daily dose groups, respectively. Eighteen, 46, and 45% of subjects achieved declines of 1.5 log_{10} or greater in HIV RNA in the three groups, respectively. Only subjects in the 25 and 50 mg twice-daily dose groups experienced reductions exceeding 2.0 log_{10} by day 14. The maximum mean reduction in HIV viral load for the 25 mg twice-daily group was observed on day 15, 24 h after the last dose (1.56 ± 0.7 log_{10}, $P < 0.001$), similar to the pattern observed with 50 mg twice a day, suggesting a sustained antiviral effect resulting from vicriviroc exposure. In all groups, a sustained antiviral effect was observed for 2–3 days after the last dose of vicriviroc. Viral load gradually returned towards baseline during follow-up.

Table 2. Mean (percentage coefficients of variation) pharmacokinetic properties of oral vicriviroc administered twice daily to HIV-1-infected patients for 14 days.

Day[a]	Dose[b] (mg)	$AUC_{0-12\,h}$ (ng h/ml)	C_{max} (ng/ml)	C_{min} (ng/ml)	T_{max}[c] (h)	$t^{1}/_{2}$ (h)	Cl/F (l/h)	Vd/F (l)
1	10 ($n = 11$)	178 (14)	39 (21)	NC	1.0 (1.0–2.0)	NC	NC	NC
	25 ($n = 13$)	487 (27)	100 (19)	NC	1.5 (1.0–2.0)	NC	NC	NC
	50 ($n = 11$)	987 (18)	203 (23)	NC	1.5 (1.0–3.0)	NC	NC	NC
14	10 ($n = 11$)	424 (34)	65 (32)	23 (48)	1.0 (0.5–2.0)	33 (16–49)	22 (34)	960 (49)
	25 ($n = 12$)	1060 (27)	149 (21)	56 (32)	1.5 (1.0–2.0)	29 (15–54)	21 (25)	854 (47)
	50 ($n = 11$)	2290 (43)	342 (35)	117 (52)	1.5 (0.5–1.5)	28 (15–40)	21 (39)	778 (25)

$AUC_{0-12\,h}$, Area under the plasma concentration-time curve from 0 to 12 h; Cl/F, total body clearance; C_{max}, maximum observed plasma concentration; C_{min}, trough plasma concentration, NC, not calculated; $t^{1}/_{2}$, terminal-phase half-life; T_{max}, time of observed maximum plasma concentration; Vd/F, apparent volume of distribution.

[a]Following the morning dose.

[b]Vicriviroc is administered as the maleate salt. Doses of 10, 25, and 50 mg vicriviroc maleate salt are equivalent to 8.2, 20.5, and 41.1 mg vicriviroc free base, respectively.

[c]Median (range).

Absolute CD4 T-cell counts

After the administration of vicriviroc, there was a suggestion of increasing numbers of absolute CD4 T-cell counts in subjects receiving vicriviroc, compared with placebo. The mean change (± SEM) from baseline in absolute CD4 cells observed on day 14 was $+60 \pm 33$ cells/μl for placebo, and $+70 \pm 36$, $+146 \pm 33$ and $+83 \pm 36$ cells/μl for the 10, 25, and 50 mg twice-daily dose groups, respectively (Table 3).

Effects on viral tropism

The tropism of each subject's HIV virus population for CCR5 or CXCR4 was first determined at screening. Viral tropism was reassessed at baseline and on days 7, 14, and 28 of the study. No subject had detectable X4 virus at screening. The emergence of detectable X4 virus was observed in two subjects in the 50 mg twice-daily treatment group. One subject was determined, in retrospect, to have had the X4-tropic virus emerge between screening and baseline before dosing; his virus remained R5/X4 mixed tropic at study completion. The R5 component of the mixed population remained sensitive to vicriviroc, and the subject exhibited an approximately $0.5 \log_{10}$ decline in HIV RNA during treatment. The second individual experienced the emergence of detectable X4-tropic virus between baseline and day 14 of dosing. This individual had a greater than $1.5 \log_{10}$ reduction in viral RNA on treatment and reverted to a R5 tropism (no detectable X4) on day 28 after the discontinuation of vicriviroc.

Safety and tolerability

Safety analyses included data for 36 subjects exposed to vicriviroc compared with 13 administered placebo. The frequency of adverse events reported after vicriviroc (72%) and placebo (62%) exposure was similar. Vicriviroc was well tolerated across the three active-dose groups, with the lowest frequency of adverse events reported at 50 mg twice a day. No dose relationship between the incidence or type of adverse event was observed. The most frequent adverse events reported by subjects on active drug included headache (28%), abdominal pain (14%), nausea (14%), and pharyngitis (11%), which were most often classified as mild in intensity and judged unlikely to be related to the study drug.

Two events were reported as serious adverse events during study drug administration, both in the 25 mg twice-daily group. One subject, determined retrospectively to have positive syphilis serology at entry, developed secondary syphilis with rash and fever 10 days after the last dose of vicriviroc. This responded to treatment with penicillin. The second subject developed a febrile illness associated with an upper respiratory infection in the first week of dosing that prolonged the protocol-specified hospitalization. Despite blood cultures and other appropriate evaluation, this event was not diagnosed specifically, but resolved while the patient was receiving empiric fluoroquinolone therapy. Neither event was judged to be clearly related to vicriviroc.

There were no consistent changes of clinical relevance observed in any of the safety parameters evaluated, including physical examination, laboratory analyses, and electrocardiogram measurements. Mild transient elevations in hepatic enzymes ($\leq 2\times$ the upper limit of normal) during treatment were observed in two subjects receiving vicriviroc (one at 25 mg twice a day and one at 50 mg twice a day) and one subject receiving placebo. None of the subjects' changes in hepatic enzymes was considered clinically significant.

No trend in electrocardiogram changes was observed, although a transient asymptomatic prolongation of the QT interval, (QTcF > 60 ms), occurred in one subject in the placebo group on day 14 and one subject in the 50 mg twice-daily treatment group on day 7. Neither of these findings was judged to be clinically relevant or apparently related to the study drug. A blinded third-party analysis of all the electrocardiograms revealed no difference in mean/median change in the QTcF interval between active dose groups and placebo after 14 days of dosing. The median change from baseline at day 14 was 2.2, −2.2, 2.6, and 1.4 ms for placebo, 10, 25 and 50 mg twice a day, respectively.

Discussion

The magnitude of HIV-RNA suppression achieved with vicriviroc in this study was similar to other CCR5 receptor antagonists in clinical development [16–21]. Among the three dose levels examined, potent dose-related antiviral activity was observed, ranging from 0.9 to $1.62 \log_{10}$ mean suppression of plasma HIV RNA after 14 days of vicriviroc monotherapy. The suppression of viral replication was measurable after the first few days of vicriviroc treatment, and reached an apparent nadir on day 10. Similar to other CCR5 receptor antagonists, the

Table 3. Change from baseline in HIV RNA and absolute CD4 cell counts after 14 days of oral vicriviroc as monotherapy.

		Vicriviroc twice a day		
Parameter	Placebo	10 mg	25 mg	50 mg
HIV RNA $\log_{10}$ (SD)	+0.14 (0.3)	−0.93 (0.7)	−1.49 (0.7)	−1.62 (0.7)
CD4 cell count (cells/μl ± SD)	+60 (89.8)	+70 (100.5)	+146 (154.4)	+83 (116.4)

reductions in viral RNA persisted for 2–3 days beyond the final dose, demonstrating a durability of viral suppression [20,21].

Pharmacokinetic analysis of vicriviroc indicated excellent oral bioavailability, with rapid absorption, low inter-subject variability, and a large apparent volume of distribution. Dosing regimens developed for this and earlier phase I clinical studies of vicriviroc were conservative and were utilized to minimize C_{max} while maintaining adequate exposure. Additional safety data at higher doses and the extended terminal half-life of 28–32 h observed in this study and other phase I studies clearly support once-daily dosing with vicriviroc [22,23].

The antiviral activity of the 25 and 50 mg twice-daily dose groups was similar overall, despite approximately twice the exposure to vicriviroc in the 50 mg twice-daily dose group. This suggests that the optimal dose in this study may be a total daily dose equivalent to 25 mg twice a day. The failure of three out of 13 and two out of 11 subjects in the 25 and 50 mg twice-daily dose groups, respectively, to achieve a decline of 1.0 $\log_{10}$ or greater in HIV RNA cannot be explained readily and may suggest that the exploration of higher doses may have merit.

Two subjects in this study demonstrated a change in viral tropism, from apparently 'pure' R5 virus to detectable mixed R5/X4 virus. Although an overall change in viral tropism from R5 virus to X4 virus may be associated with accelerated HIV disease progression, whether this is a cause or effect relationship is not currently known. In this short study, no conclusions could be drawn regarding the clinical relevance of this finding. Both patients' viral loads decreased, however, and CD4 T-lymphocyte counts increased on vicriviroc therapy.

Vicriviroc was well tolerated across the range of total daily doses from 20 to 100 mg administered as two divided doses. Safety analyses of clinical laboratory and electrocardiogram assessments performed throughout the study period revealed no significant findings. The two adverse events categorized as serious were deemed to be 'possibly related' to the study drug because of the theoretical possibility that blockade of the CCR5 chemokine receptor might have immunomodulatory consequences [24,25]. Although plausible, this speculation is not supported by any observed immunosuppressive effects of vicriviroc in preclinical testing. The potential for immunomodulation in humans warrants continued monitoring as the clinical development of agents that inhibit both CCR5 and CXCR4 chemokine receptor antagonists progresses [26].

Several conclusions can be drawn from this short vicriviroc dose-finding study. Fourteen days of 25 or 50 mg twice-daily oral dosing resulted in a potent suppression of HIV viral replication, which was similar between the two dose groups and was significantly greater than was observed with the lower dose of 10 mg twice a day, suggesting that the higher doses may be nearing the plateau of the dose–response curve. The small number of individuals who did not respond to these dose levels raises the possibility that even higher doses may be useful in some patients.

Once daily dosing is fully supported by the pharmacokinetics of vicriviroc and will provide a more convenient dosing regimen. Cumulatively, the results of safety and antiviral activity from this study demonstrate the potential of vicriviroc as a new treatment for HIV-infected patients, and support its continued clinical development as a once-daily oral agent in combination regimens of antiretroviral agents. Because it is a substrate of CYP3A4, the use of vicriviroc with ritonavir-containing regimens is under study.

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