STUDY 202 (PK/PD ANALYSIS)

Exposure-Response Relationship of Cenicriviroc with Week 24 Virologic Outcomes in Treatment-Naïve HIV-1-Infected Adults with CCR5-Tropic Virus

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Background

- Cenicriviroc (CVC) is a novel, once-daily, potent, CCR5 and CCR2 antagonist that has recently completed Phase 2b evaluation for the treatment of HIV-1 infection in treatment-naïve adults (Study 202; NCT01338883).[a]
- The Week 24 primary analysis of the Phase 2b, dose-finding study comparing CVC 100 mg and 200 mg with efavirenz (EFV), in combination with emtricitabine/tenofovir (FTC/TDF), demonstrated favourable tolerability for CVC and comparable virologic success (HIV-1 RNA <50 copies/mL; FDA Snapshot) for CVC (73–76%) and EFV (71%). Virologic non-response was higher with CVC (12–14%) than with EFV (4%).[1]
- The current preplanned pharmacokinetics (PK)/pharmacodynamics (PD) analyses of the Phase 2b study were carried out to assess the PK of CVC, using a population approach, and to determine the relationship between CVC exposure and virologic outcomes at Week 24.

[a]Note that the Week 48 analysis from this Phase 2b study will be presented at this conference (Feinberg *et al*.; Abstract PS4/1).

Methods

Study Design

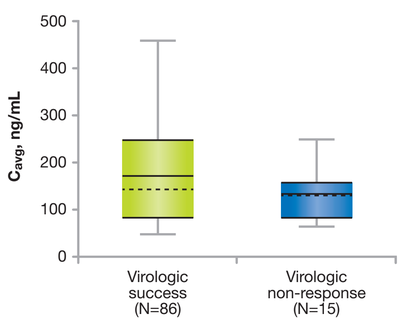
- In Study 202, a double-blind, double-dummy study in HIV-1-infected, treatment-naïve adults with CCR5-tropic virus, subjects were randomised to receive CVC 100 mg once daily (qd), CVC 200 mg qd or EFV 600 mg qd, plus open-label FTC/TDF for 48 weeks.
- Of 143 subjects randomised, 115 were treated with CVC, of whom 110 had at least one measurable CVC concentration and were included in the population PK analysis.
  - There were 18 subjects with 24-hour sampling on Day 14 (rich samples) and 92 subjects with trough and/or random sampling (sparse samples).
  - Trough samples were collected in all subjects before CVC doses on Day 1 and at Weeks 4, 24 and 48.

PK/PD Analyses

- A pre-planned population PK analysis was performed by integrating the rich and sparse samples collected during the study until Week 24, as part of the Week 24 primary analysis.
- A 2-compartmental population PK model was derived from the rich samples and subsequently used to predict individual CVC exposures from the sparse samples.
- To assess the relationship between CVC exposure parameters and Week 24 virologic outcomes (FDA Snapshot algorithm), individual average (C_{avg}) and minimum (C_{min}) plasma CVC concentrations were predicted with the model and used to conduct PK/PD analyses.
  - C_{avg} over 24 weeks of treatment (or for a shorter duration in the event of premature withdrawal).
  - C_{min} at Week 24 (if no PK data were available at Week 24, the last predicted C_{min} was carried forward).
- Virologic response was analysed at Week 24 using the FDA Snapshot algorithm. Virologic success was defined as a last on-treatment HIV-1 RNA value in the Week 24 window (between study days 154–182 inclusive) of <50 copies/mL and no disallowed change in antiviral therapy prior to that time point.
- Exposure-response relationships were assessed in 101 subjects; CVC-treated subjects who prematurely discontinued the study for non-virologic reasons were excluded.

Figures and Tables

Figure 1. Predicted Average Plasma CVC Concentrations (C_{avg}) versus Week 24 Virologic Outcomes[a]



[a]The lower and upper edges of the boxes represent the 25th and 75th percentiles, respectively; the solid and dashed lines represent the mean and median, respectively. The whiskers show the lowest data value still within 1.5 interquartile range (IQR) of the lower quartile, and the highest value still within 1.5 IQR of the upper quartile, where IQR is the difference between the third and first quartiles (middle 50%). Data values that do not fall between the whiskers are plotted as outliers

Figure 2. Predicted Average Plasma CVC Concentrations (C_{avg}) versus Week 24 Virologic Outcomes, Proportion of Subjects, %

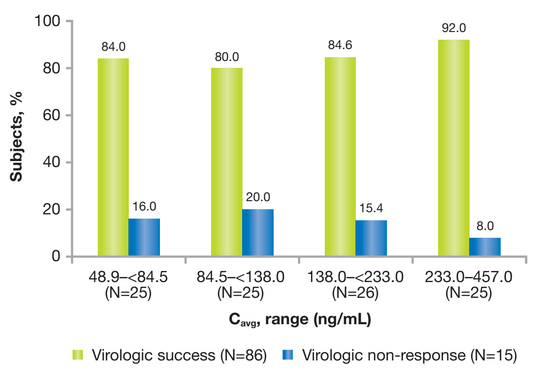


Figure 3. Predicted Minimum Plasma CVC Concentrations (C_{min}) versus Week 24 Virologic Outcomes[a]

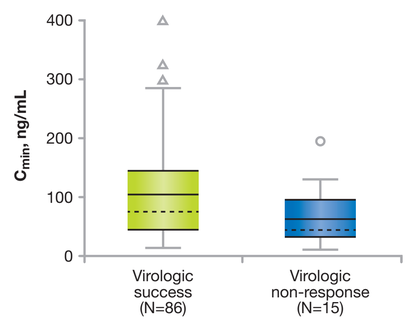


Figure 4. Predicted Minimum Plasma CVC Concentrations (C_{min}) versus Week 24 Virologic Outcomes, Proportion of Subjects, %

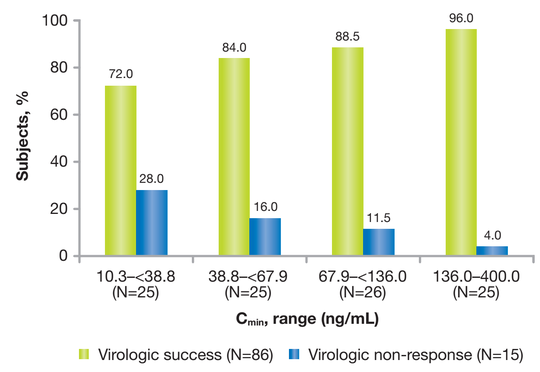


Figure 5. Classification and Regression Tree (CART) Analysis of the Association between C_{min} and Virologic Outcomes

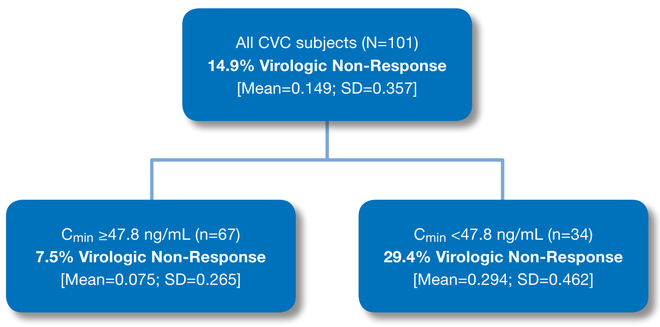


Figure 6. Predicted Week 24 C_{min} Data for Both CVC Doses Evaluated in Study 202

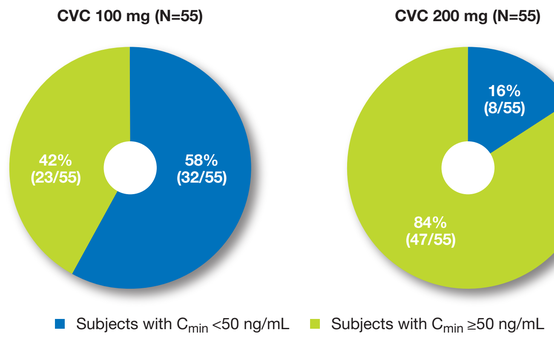


Table 1. CVC Exposure Parameters and Virologic Outcomes at Week 24

Week 24 outcomes (Snapshot)	Statistic	C_{avg} (ng/mL)	C_{min} (ng/mL)
Virologic success (N=86)	Median	144.5	74.9
	Mean	172.2	102.7
	CV%	59%	80%
Virologic non-response (N=15)	Median	132.0	42.9
	Mean	134.5	60.9
	CV%	43%	80%
P value[a]		0.31	0.029

[a]Mann–Whitney U test
CV, coefficient of variation

Results

- Summary of plasma CVC concentrations showed that steady-state concentrations were reached by Day 14 (in the subjects with rich sampling), and that levels were relatively constant through 24 weeks (in the subjects with sparse sampling) (data not shown). Plasma CVC concentrations were generally dose-proportional.[2]

Predicted C_{avg} and C_{min} vs Week 24 Virologic Outcomes

- The relationship between CVC C_{avg} and Week 24 virologic response is shown in Figure 1. The median C_{avg} was slightly greater in subjects who experienced virologic success at Week 24 than in non-responders (144.5 vs 132.0 ng/mL, respectively) (Table 1).
- The determination of virologic outcomes at Week 24 for each quartile of CVC C_{avg} values showed a slight trend toward improved virologic outcomes with increasing average exposures (Figure 2).
- The relationship between CVC C_{min} and Week 24 virologic response is shown in Figure 3. The median CVC C_{min} in virologic non-responders at Week 24 was approximately 43% lower than in subjects who experienced virologic success at Week 24 (42.9 vs 74.9 ng/mL, respectively) (Figure 3; Table 1).
- A more pronounced trend toward improved virologic outcomes was observed with increasing minimum exposures.
  - There were more subjects with virologic success at Week 24 with higher CVC C_{min} values than with lower CVC C_{min} values (Figure 4).
- Although not present for C_{avg}, there was a statistically significant difference between C_{min} values for subjects categorised as Week 24 virologic successes versus non-responders (Table 1).
- In conclusion, the Study 202 data suggest an exposure-response relationship with virologic outcomes, with predicted C_{min} having the strongest correlation. C_{min} was therefore investigated further in more detailed exposure-response assessments.

C_{min} Breakpoint

Classification and Regression Tree (CART) Analysis

- A CART analysis was performed to further investigate the association between C_{min} and virologic outcomes, again excluding early discontinuations for non-virologic reasons.
- A statistically significant split occurred at a C_{min} value of 47.8 ng/mL (Figure 5).
  - 67 subjects had C_{min} values ≥47.8 ng/mL and the proportion of virologic non-responders in this subset was 7.5%.
  - 34 subjects had C_{min} values <47.8 ng/mL and the proportion of virologic non-responders in this subset was 29.4%.

E_{max} Model

- A simple E_{max} model was used to describe the relationship between C_{min} and virologic outcome; an EC_{50} of 44.7 ng/mL was derived from this model, which was consistent with the C_{min} breakpoint (47.8 ng/mL).
  - These breakpoints were similar to the EC_{90} of 46.8 ng/mL derived from the Phase 2a proof-of-concept CVC monotherapy study (Study 652-2-201; NCT01092104[3]).

Predicted C_{min} Data for CVC 100 mg and 200 mg Doses

- When the PK model was used to predict C_{min} data for both doses of CVC, it was shown that 58% of subjects receiving CVC 100 mg would have C_{min} below 50 ng/mL compared to only 16% of subjects receiving CVC 200 mg (Figure 6).

CVC Exposure in Subjects with Emerging NRTI Resistance-Associated Mutations

- An exploratory pharmacological assessment was conducted in the 5 CVC-treated subjects who met protocol-defined virologic failure (at any time during the study) and who had treatment-emergent nucleoside reverse transcriptase inhibitor (NRTI) resistance-associated mutations.
- All emerging primary NRTI mutations occurred at codon 184. In 4 of 5 subjects with emerging substitutions at codon 184, predicted C_{min} values were below 50 ng/mL.

Conclusions

- When given with FTC/TDF in treatment-naïve HIV-1-infected adults, CVC was effective at daily doses of 100 mg and 200 mg.[1,4]
- PK/PD analyses at Week 24 revealed an exposure-response relationship for CVC, where higher C_{min} was associated with improved virologic outcomes.
- A CART analysis revealed a CVC C_{min} breakpoint concentration of 47.8 ng/mL; subjects reaching or exceeding this concentration were much less likely to experience virologic non-response at Week 24 than those with lower concentrations (7.5% vs 29.4%, respectively).
- Four of five CVC-treated subjects with protocol-defined virologic failure (at any time during the study) and emerging NRTI resistance-associated mutations had C_{min} <50 ng/mL.
- Predicted C_{min} data for the two CVC dose levels tested showed that there were fewer subjects with C_{min} <50 ng/mL at the 200 mg dose level than at the 100 mg dose level.
- Altogether, these data (with the efficacy and safety data from the Week 48 analysis) support the selection of the CVC 200 mg dose for Phase 3 evaluation.

Acknowledgements: The authors would like to thank all study participants. Assistance was provided by Sandra Whitelaw, Alpharmaxim Healthcare Communications.

References: 1. Gathe J, Cade J, DeJesus E, *et al*. Week 24 primary analysis of cenicriviroc vs efavirenz, in combination with FTC/TDF, in treatment-naïve HIV-1 infected adults with CCR5-tropic virus (Study 652-2-202; NCT01338883). Presented at 20th Conference on Retroviruses and Opportunistic Infections, March 2013, Atlanta, GA, USA. Oral presentation 106LB; **2.** Martin D, Beliveau M, Marier JF, *et al*. Pharmacokinetics (PK) of cenicriviroc (CVC) following 100 or 200 mg once-daily dosing with open-label tenofovir/emtricitabine (TDF/FTC) in HIV-1-infected subjects enrolled in a Phase 2b study. Presented at 19th Conference on Retroviruses and Opportunistic Infections, March 2012, Seattle, WA, USA. Poster 600; **3.** Lalezari J, Gathe J, Brinson C, *et al*. Safety, efficacy, and pharmacokinetics of TBR-652, a CCR5/CCR2 antagonist, in HIV-1-infected, treatment-experienced, CCR5 antagonist-naive subjects. *J Acquir Immune Defic Syndr* 2011;57(2):118–125; **4.** Feinberg J, Thompson M, Cade J, *et al*. Final Week 48 Analysis of Cenicriviroc (CVC) Compared to Efavirenz (EFV), in Combination with Emtricitabine/Tenofovir (FTC/TDF), in Treatment-Naïve HIV-1-Infected Adults with CCR5-Tropic Virus. Abstract PS4/1

We will also present the following studies for cenicriviroc at EACS 2013:

- Feinberg J, *et al*. Final Week 48 Analysis of Cenicriviroc (CVC) Compared to Efavirenz (EFV), in Combination with Emtricitabine/Tenofovir (FTC/TDF), in Treatment-Naïve HIV-1-Infected Adults with CCR5-Tropic Virus. Abstract PS4/1 [Oral presentation]
- Lefebvre E, *et al*. Pharmacokinetic Interactions between Cenicriviroc and Dolutegravir. Abstract PE10/8 [Poster presentation]
- Lefebvre E, *et al*. Pharmacokinetic Interactions between Cenicriviroc and Darunavir/Ritonavir. Abstract PE10/9 [Poster presentation]

Poster presented at 14th European AIDS Conference (EACS), Brussels, Belgium, 16–19 October 2013