

Title:

Cerebrospinal fluid exposure of cenicriviroc in HIV-positive individuals with cognitive impairment

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Abstract**Background:**

Cenicriviroc, a dual C-C chemokine receptor type 2 (CCR2) and type 5 (CCR5) antagonist, is a potential adjunctive therapy, along with antiretroviral therapy (ART), for the management of HIV-associated cognitive disorders.

Materials and Methods:

Virologically suppressed persons living with HIV (PLWH) with a clinical diagnosis of HIV-related cognitive impairment intensified ART with cenicriviroc once daily, dose dependent on current ART, for eight weeks. Subjects with current or previous use of CCR5 inhibitors were not eligible. We assessed cerebrospinal fluid (CSF) exposure of cenicriviroc and CSF albumin at week 8, and changes in cognitive function over 8 weeks.

Cenicriviroc concentration was determined using reverse phase high-performance liquid chromatography (HPLC) with geometric mean (GM) and 95% confidence intervals (CI) calculated. The proposed cenicriviroc target concentration was above the 90% effective concentration (EC_{90}) for cenicriviroc (0.17 ng/mL), with the lower limit of quantification (LLQ) 0.24 ng/mL taken as target concentration. Cognitive function assessment comprised of seven domains with composite Z-scores reported.

Results:

Four of seven enrolled participants completed all study procedures. Median age was 43 years (interquartile range (IQR) 39 - 47), current CD4+ count 375 cells/ μ L (IQR 315 - 555) and plasma HIV RNA undetectable in all. At week eight, CSF exposure was detected in two subjects (0.82 and 0.40 ng/mL) and below the LLQ in two (*see Table*). Mean CSF: plasma cenicriviroc concentration ratio was no more than 0.18% (95% CI of the upper estimate 0.09% - 0.28%). Median CSF: serum albumin ratio was 10.1 (IQR 7.2-19.5) and CSF albumin was higher in those with detectable cenicriviroc in the CSF. Overall cognitive performance Z-score was -0.14 (95% CI -1.35 to 1.07) at baseline, and -0.27 (95% CI -1.70 to 1.17) at week 8.

Conclusion:

In PLWH with cognitive impairment, cenicriviroc CSF exposure is close to the EC_{90} .

Table

Subject	1	2	3	4
Cenicriviroc concentration				
CSF, ng/mL	0.82	0.40	0.24 (<LLQ)	0.24 (<LLQ)
Plasma, ng/mL	718.6	211.1	411.9	70.5
CSF: plasma cenicriviroc concentration ratio (%)	0.11	0.19	0.06	0.34
Albumin concentration				
CSF, mg/L	1070	453	374	202
Serum, g/L	38	42	40	40
CSF: serum albumin ratio	28.2	10.8	9.4	5.1
Antiretroviral therapy	abacavir, lamivudine, raltegravir	lamivudine, atazanavir, ritonavir	tenofovir DF, emtricitabine, dolutegravir	tenofovir DF, emtricitabine, raltegravir
Cenicriviroc dose	150 mg	50 mg	150 mg	150 mg

Table legend:

Abbreviations used: CSF = cerebrospinal fluid, tenofovir DF = tenofovir disoproxil fumarate, LLQ = lower limit of quantification