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

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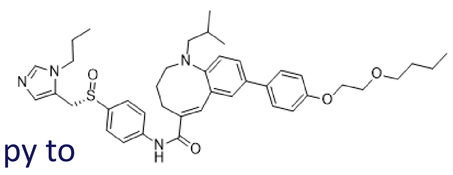
BACKGROUND

- HIV-associated cognitive impairment remains prevalent despite effective plasma viral suppression with cART[1]
- Ongoing neuroinflammation is postulated to be a major underlying cause[2]
- At present, there are no proven interventions for the management of cognitive impairment in people living with HIV[3]
- Cenicriviroc is a novel dual CCR2 and CCR5 antagonist, and is hypothesised to have both antiretroviral[4] and anti-inflammatory activity[5]
- Thus, cenicriviroc is a potential adjunctive therapy to cART for the management of HIV-associated cognitive impairment



OBJECTIVES

- To determine cerebrospinal fluid exposure of cenicriviroc in people living with HIV (PLWH) with symptomatic cognitive impairment
- Assessment of safety, tolerability and cerebral function parameters

METHODS: STUDY DESIGN

- Phase II, open label descriptive study assessing the effects of eight weeks cART intensification with cenicriviroc
- Inclusion criteria: HIV-positive patients suppressed on cART with symptomatic cognitive impairment
- Exclusion criteria: Pre-existing neurological or significant psychiatric co-morbidities and those on current or previous CCR5 inhibitors

METHODS: STUDY PROCEDURES

- Cognitive testing was performed at baseline and week 8 (CogState™ battery), which included a detailed assessment of 7 cognitive domains
- Following cerebral magnetic resonance imaging, lumbar puncture was performed at baseline and week 8, with paired plasma sampling
- Cenicriviroc concentration was determined using a reverse phase high-performance liquid chromatography (HPLC) & mass spectrometry
- EC_{90} for cenicriviroc is 0.17 ng/mL, and LLQ for cerebrospinal fluid cenicriviroc concentration (0.24ngl/mL) was utilised as target concentration
- Cerebrospinal fluid (mg/L): serum (g/L) albumin ratio was used as a surrogate measure of blood-brain barrier integrity

RESULTS: BASELINE and FOLLOW UP PARAMETERS

	All subjects	Subjects who completed study	
	Baseline	Baseline	Week 8
Number of subjects	7	4	4
Age, years	45 (42 – 49)	43 (39 – 47)	
CD4 count, cells/µL	715 (375 – 788)	375 (315 – 555)	495 (302 – 660)
Nadir CD4 count, cells/µL	230 (205 – 265)	205 (175 – 220)	
CSF parameters			
HIV RNA ≤20 copies/mL	7 (100)	4 (100)	4 (100)
Protein, mg/dL	0.70 (0.41 – 0.77)	0.76 (0.54 – 1.02)	0.58 (0.44 – 0.94)
CSF: serum albumin ratio	8.4 (6.7 – 13.7)	13.7 (8.9 – 18.9)	10.1 (7.2 – 19.5)
Cenicriviroc concentration[1]			
Plasma, ng/mL	<LLQ	<LLQ	353 (141 – 592)
CSF, ng/mL	<LLQ	<LLQ	0.43 (0.28 – 0.68)
CSF: Plasma ratio (%)	<LLQ	<LLQ	0.18 (0.09 – 0.28)
Computerised cognitive test[2]			
Composite Z-score	0 (-0.57 – 0.57)	-0.14 (-1.35 – 1.07)	-0.27 (-1.70 – 1.17)
Composite Z-score change			-0.13 (-0.73 – 0.48)

Values are total or median (% or IQR) unless stated otherwise

[1] geometric mean (95% CI), [2] mean (95% CI)

IQR = interquartile range; CSF = cerebrospinal fluid; LLQ = lower limit of quantification; CI = confidence interval

WEEK 8 RESULTS	Subject 1	Subject 2	Subject 3	Subject 4
Cenicriviroc concentration				
CSF, ng/mL	0.82	0.40	0.24 (<LLQ)	0.24 (<LLQ)
Plasma, ng/mL	718.6	211.0	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

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

KEY RESULTS and CONCLUSIONS

- In HIV-positive subjects on suppressive cART with cognitive impairment, mean cerebrospinal fluid: plasma cenicriviroc concentration ratio was no more than 0.18% and cenicriviroc cerebrospinal fluid exposure was close to the EC_{90}
- Whether this is sufficient exposure for antiretroviral and anti-inflammatory activity within the central nervous system needs to be determined
- Participant early withdrawal rate in our neurologically symptomatic cohort was higher compared to larger studies assessing cenicriviroc in asymptomatic PLWH
- Participants with detectable cerebrospinal fluid cenicriviroc concentration had higher cerebrospinal fluid: serum albumin ratios, indicating more disruption to the blood-brain barrier integrity

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