Highlight Sheet Study CTNPT 047 Dr Jean-Pierre Routy / Dr Stephane Isnard (Postdoctoral fellow)

Title: Influence of a 3-month letermovir treatment on gut inflammation in ART-treated HIV-infected persons in an open labelled controlled randomized study

Primary Objective: To assess the influence of CMV replication inhibition with letermovir on gut translocation markers (LPS) in blood of PLWH.

Secondary Objectives: To assess the influence of CMV replication inhibition with letermovir on:

- Gut permeability markers in blood of PLWH (REG3α and I-FABP).
- Inflammation markers (IL-6, sCD14, hsCRP, d-dimers) in blood of PLWH.
- Anti-CMV immune response (anti-CMV IgG titers and specific T-cell response) and CMV DNA detection in plasma and PBMCs
- In a sub-study, in inflammation in colon biopsies obtained by coloscopy and in CMV DNA detection in gut mucosa
- To assess the safety and tolerability of letermovir by evaluating adverse events, weight, waist circumference, hematology, serum chemistries, HIV virology and immunology over the course of the study.

Study Design: Multi-centre, open-label, randomized, controlled clinical trial

Population: Male or female, ≥18 years of age; Documented HIV-1 infection on ART for at least 3 years, Undetectable viral load <50 copies/mL for the past 3 years (viral blips below 200 copies/ml are allowed), CD4 count >400 cells/uL, CMV seropositive

Target N = 60 (40 treated, 20 controls)

Sites (4): Chronic Viral Illness Service (CVIS) at McGill University Health Centre (QI: J-P Routy)

CHU-Montreal (QI: C Tremblay) – On HOLD

CHU-de-Quebec (QI: G Boivin) – On HOLD

Intervention: Anti-CMV specific drug: MK-8228 (letermovir) 480mg (14 weeks)

Randomization: 2:1 Ratio Treatment (letermovir/MK-8228): Standard of Care

Study Duration: Participants on study for 26 weeks from Baseline 2 (randomization)

Enrolment Period: July 2022 – June 2026; (study suspended in July 2024 for interim analysis, resumption of enrolment in 2025 dependent on results of IA; study terminated Mar 2025 based on results of IA and recommendation from DSMC to cease further enrolment)

Study Period: July 2022- December 2026

CTN In-kind Services:

* Project Management

* Data Management

* Randomization system

* Regulatory (Health Canada, Risk Register)

* Statistics & Methodology

Visit Schedule/Procedures:

Visit Type	Screening	Study Visits					
		Baseline 1	Baseline 2	Treatment			Post-treatment
Visit Window **Procedures:**	**Week -5 to -1**	**Week -2 (±7 days)**	**Week 0 (Day 0)**	**Week 2 (±3 days)**	**Week 4 (±3 days)**	**Week 14 (±7 days)**	**Week 26 (±7 days)**
Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Informed Consent	X						
Oral re-consent		X					
Eligibility Assessment	X	X	X				
Concomitant Medication	X	X	X	X	X	X	X
Medical History	X						
Complete Physical Exam,Vital Signs & Waist Circumference	X						
Targeted Physical Exam‡,Vital Signs & Waist Circumference		X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X
Serum Pregnancy Test	X	X	X	X	X	X	X
Hematology*	X	X†	X	X	X	X	X
Serum Chemistry**	X	X†	X	X	X	X	X
Serology***	X		X				
Serology - HIV-1 Viral Load****	X	X†	X	X	X	X	X
Markers of gut barrier integrity, inflammation and microbial translocation++		X	X	X	X	X	X
Immune activation markers/cytokines (ELISA)****		X	X	X	X	X	X
Monocyte and T cell activation markers+		X	X	X	X	X	X
Anti-CMV IgG and IgM in Serum, anti-CMV CD4 and CD8 T-cells in PBMC, CMV DNA in plasma and PBMC		X	X	X	X	X	X
Size of HIV reservoir in Latently Infected CD4 T cells+++		X	X	X	X	X	X
Stool sample collection and microbiota composition++++		X	X	X	X	X	X
Alcohol use (AUDIT-Full), Appendix 1	X						
Alcohol use (AUDIT-C), Appendix 2		X	X	X	X	X	X
Bristol score questionnaire, Appendix 5	X	X	X	X	X	X	X
Investigational Product Dispensation#			X	X	X		
Dispense Dosing Diary#			X				
Collect Dosing Diary#				X	X	X	
Investigational Product Compliance#				X	X	X	
Colon mucosal biopsies##			X			X	

*CBC, CD4 and CD8 T cell counts, erythrocyte sedimentation rate (ESR).

**Alkaline phosphatase, ALT, Amylase, AST, Bilirubin (total), Creatine kinase, Creatinine, D-dimer, fasting blood glucose, HbA1c, high sensitivity C-reactive protein (hsCRP), Lipase, lipid profile (total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), Triglycerides), serum phosphate

***Serology measurements include: Cytomegalovirus (CMV), Hepatitis B virus (HBV), HCV and HIV viral load. Since HIV viral load will be measured at each visit, it was put as a separate line item.

****Immune activation markers/cytokines include: soluble CD14, pro-inflammatory cytokines (IL-1β, IL-6, IL-8, TNF-α) and anti-inflammatory cytokine IL-10. Measured in plasma by ELISA.

+Monocyte and T-cell activation markers include: HLA-DR and CD38. T-cell exhaustion marker: PD-1. Measured by staining and flow cytometry.

++Markers of gut barrier integrity, microbial translocation and inflammation: LPS, BDG, sCD14, I-FABP, Reg3a (measured in plasma by ELISA).

+++PBMCs will be isolated and then latent CD4 T-cells will be isolated by flow cytometry. HIV viral reservoir in the latent CD4 T-cell population will be measured by nested qPCR. More specific TILDA analysis will be performed on Baseline Week 0 and End-treatment Week 14 samples to assess the HIV viral reservoir (Exploratory analysis).

++++qPCR of A. muciniphila, 16S and 18S rDNA sequencing for other members of the microbiota.

#Treatment arm only

##Optional sub-study procedure.

† Not required when the same tests have been performed at the screening visit within the past 14 days, with the exception of CBC, CD4, CD8 (and serum pregnancy test)

‡ If required