PRO 140 (leronlimab) SC: Long-Acting Single-Agent Maintenance Therapy (SAMT) for HIV-1 Infection

Kush Dhody[1], Kazem Kazempour[1], Nader Pourhassan[2] and Paul J. Maddon[3]

[1]Amarex Clinical Research, LLC, Germantown, MD [2]CytoDyn Inc., Vancouver, WA, [3]Maddon Advisors LLC, Scarsdale, NY

Introduction

- PRO 140 (leronlimab) is a humanized IgG4 monoclonal antibody that blocks HIV-1 from entering and infecting immune cells by binding to CCR5 with high affinity
- Potently inhibits CCR5-mediated HIV-1 entry without blocking the natural activity of CCR5 *in vitro*
  - High genetic barrier to virus resistance
- PRO 140 (leronlimab) broadly inhibits genotypically diverse viruses *in vitro*
  - Wild-type and multidrug-resistant HIV-1
  - Viruses resistant to maraviroc (SELZENTRY®)
  - Both laboratory and low-passage clinical strains
- PRO 140 has been administered intravenously or subcutaneously to more than 650 healthy and HIV-1 infected individuals in Phase I/II/III studies showing potent, long-term antiviral activity in clinical studies.
- No dose-limiting toxicity in animals and generally well tolerated following intravenous administration of single doses of 0.5 to 10 mg/kg or up to 700 mg weekly doses as subcutaneous (SC) injection in clinical studies. The longest duration of exposure lasting more than 4 years at 350 mg SC weekly dose.
- Designated FDA Fast Track drug candidate

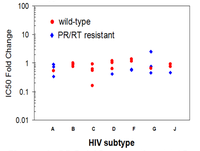


Figure 1. PRO 140 (leronlimab) IC_{50} Fold Changes For HIV Subtypes

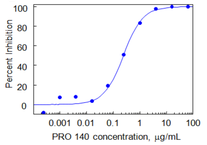


Figure 2. PRO 140 (leronlimab) Concentration - Viral Inhibition Curve

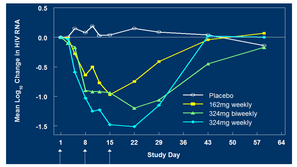


Figure 3. Antiviral Activity of Short-Term Monotherapy with PRO 140

Objectives

- The CD03 study was designed to assess the clinical safety and treatment strategy of PRO 140 (leronlimab) SC as a long-acting, single-agent, maintenance therapy in virally suppressed HIV-1 patients with CCR5-tropic HIV-1 receiving combination antiretroviral therapy.

Methods and Materials

- Patients were shifted from combination antiretroviral regimen to weekly PRO 140 (leronlimab) monotherapy for 48 weeks during the Treatment Phase with the one week overlap of existing retroviral regimen and PRO 140 (leronlimab) at the beginning of the study treatment.
- Patients who experienced virologic failure were given the option of receiving a higher dose of PRO 140 under rescue arm or returning to their prior ART regimen .
- The first ~150 eligible subjects were enrolled to receive PRO 140 (leronlimab) 350mg SC weekly injection in a single-arm study. Subsequently, next ~150 subjects were randomized 1:1 to PRO 140 (leronlimab) 350mg (Group A) or PRO 140 (leronlimab) 525mg (Group B). An additional ~200 subjects will be randomized 1:1 to PRO 140 (leronlimab) 525mg (Group B) or PRO 140 (leronlimab) 700mg (Group C).

Key Inclusion Criteria

- Age ≥18 years
- Receiving combination antiretroviral therapy for last 24 weeks
- Exclusive R5-tropic virus (Trofile™ DNA Assay)
- Plasma HIV-1 RNA <50 c/mL at Screening and no documented detectable viral loads (>50 c/mL) within the last 24 weeks prior to Screening
- Nadir CD4 count >200 cells/mm^3
- CD4 count >350 cells/mm^3 at in preceding 24 weeks and at Screening

Key Exclusion Criteria

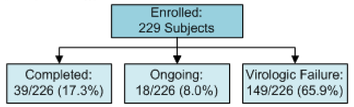
- Hepatitis B
- A history of an AIDS-defining illness
- ≥ Grade 4 DAIDS lab abnormality

Baseline Characteristics

		PRO 140 (leronlimab)		
		350 mg	525 mg	700 mg
Parameter	Statistic	N=227	N=115	N=43
Age	Mean (SD)	49.9 (12.5)	49.3 (12.0)	49.4 (11.7)
Gender	Male, n(%)	183 (81.0%)	87 (75.7%)	34 (79.1%)
Race	Caucasian, n(%)	149 (65.9%)	59 (51.3%)	31 (72.1%)
Time since HIV Diagnosis (yrs)	Mean (SD)	17.1 (9.57)	15.1 (10.3)	14.6 (10.0)
Years of HAART	Mean (SD)	15.1 (8.93)	12.7 (8.26)	12.3 (9.10)

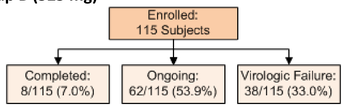
Results

Group A (350 mg)



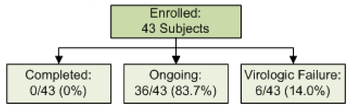
Note: 20 subjects were early terminated from the study.
3 subjects were randomized, not treated

Group B (525 mg)



Note: 7 subjects were early terminated from the study.

Group C (700 mg)

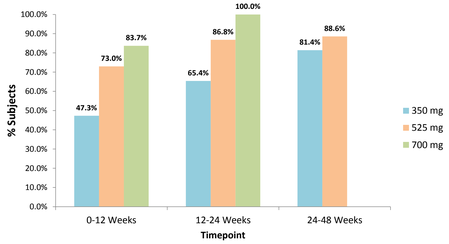


Note: 1 subject was early terminated from the study.

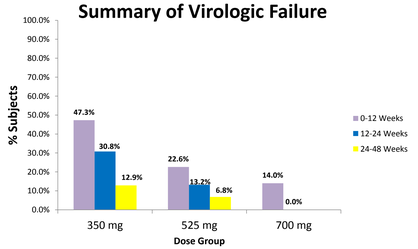
Virologic failure is defined as two consecutive plasma HIV-1 RNA levels of ≥200 c/mL.

Efficacy

Summary of Virologic Suppression



Summary of Virologic Failure



** There are no enrolled subjects in the study beyond 24 weeks as of 1 Jan 2019. Subjects are currently ongoing.*

Safety Summary

Summary of Adverse Events (AEs) by Severity

	PRO 140 (leronlimab)		
	350 mg	525 mg	700 mg
Parameter	N=226	N=115	N=43
Total # of subjects with ≥1 AE	170 (75.2%)	65 (56.5%)	21 (48.8%)
Total Number of AEs	983	314	69
Mild	62 (27.4%)	33 (28.7%)	16 (37.2%)
Moderate	90 (39.8%)	28 (24.3%)	4 (9.3%)
Severe	18 (8.0%)	3 (2.6%)	1 (2.3%)
Missing	0 (0.0%)	1 (0.9%)	0 (0.0%)

All percentages are based on the number of subjects in the treatment group(N).
A subject is counted only once within each category.

Summary of AEs by Relationship

	PRO 140 (leronlimab)		
	350 mg	525 mg	700 mg
Parameter	N=226	N=115	N=43
Total Number of Subjects with ≥1 AE	170 (75.2%)	65 (56.5%)	21 (48.8%)
Total Number of AEs	983	314	69
Definitely Related	42 (18.6%)	21 (18.3%)	5 (11.6%)
Probably Related	14 (6.2%)	0 (0.0%)	1 (2.3%)
Possibly Related	35 (15.5%)	2 (1.7%)	1 (2.3%)
Unlikely	22 (9.7%)	12 (10.4%)	7 (16.3%)
Unrelated	57 (25.2%)	30 (26.1%)	7 (16.3%)

All percentages are based on the number of subjects in the treatment group (N).
A subject is counted only once within each category.

Summary of Serious Adverse Events (SAEs)

	PRO 140 (leronlimab)		
	350 mg	525 mg	700 mg
Parameter	N=226	N=115	N=43
Number of subjects with any reported SAE, n(%)	19 (8.4%)	4(3.5%)	2 (4.7%)
Incidence of all SAEs	23	5	2

All percentages are based on the number of subjects in the treatment group (N).
A subject is counted only once within each category.

Injection Site Reactions (ISR)

	PRO 140 (leronlimab)		
	350 mg	525 mg	700 mg
Parameter	N=226	N=115	N=43
Total Number of Subjects with ≥ Injection Site Reaction	59 (26.1%)	19 (16.5%)	1 (2.3%)
Total Number of Injection Site Reactions	164	78	1

All percentages are based on the number of subjects in the treatment group (N).
A subject is counted only once within each category.

- None of the reported SAEs were definitely or probably related to PRO 140 (leronlimab).
- Overall, the majority of AEs were considered mild in nature.
- Approximately 95% of injection site reactions were mild in intensity and considered to be self-resolving.
- There were no patterns of drug-related toxicities observed.
- No dose-proportional increase in incidence and severity of AEs were reported with higher doses of PRO 140.

Conclusions and Path Forward

- Based on preliminary results, the majority of patients receiving higher doses of PRO 140 (leronlimab) (525 or 700 mg) as single-agent maintenance therapy (SAMT) were able to maintain virologic suppression.
- Pharmacokinetic parameters demonstrated dose-proportionality over the range of three doses tested in this study.
- Additionally, there were no significant anti-drug antibodies to PRO 140 (leronlimab) detected in subjects.
- Now that response rates for higher doses are more closely aligned with standard of care, in combination with its excellent safety profile, PRO 140 (leronlimab) could be a paradigm shift in the treatment of HIV as a single-agent maintenance therapy.
- In 2019, CytoDyn is targeting a BLA submission for PRO 140 (leronlimab) in treatment of HIV-1 in treatment-experienced patients with CCR5-tropic virus and demonstrated evidence of HIV-1 replication despite ongoing antiretroviral therapy with documented genotypic or phenotypic multi-drug resistance. As the results from the recently completed CD02 study demonstrated that the proportion of subjects in the PRO 140 (leronlimab) group with reductions ≥ 0.5 log10 copies/mL was significantly higher than subjects in the placebo group (p=0.0032).
- The safety of PRO 140 (leronlimab) has been tested in over 650 subjects, providing a strong foundation for upcoming clinical trials for cancer and graft vs. host disease (GvHD) indications.

Contact: Nader Pourhassan, President & CEO, CytoDyn Inc. Email: npourhassan@cytodyn.com, Phone: 503-348-4173

Kush Dhody, Vice President, Clinical Operations, Amarex Clinical Research, LLC, Email: kushd@amarexcro.com, Phone:301-956-2536