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Final Results of the Pivotal Study of PRO 140 SC in Heavily Treatment-Experienced HIV Patients

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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 viral resistance
- PRO 140 inhibits genotypically diverse CCR5 tropic viruses with *in vitro* IC90s in the range of 10-50 nM
  - Wild-type and multidrug-resistant HIV-1
  - Viruses resistant to maraviroc (SELZENTRY®)
  - Both laboratory and low-passage clinical strains
- No dose-limiting toxicity in animals
- PRO 140 has been administered intravenously or subcutaneously to more than 700 healthy and HIV-1 infected individuals in Phase I/II/III studies showing potent, long-term antiviral activity *in vivo*.
- Designated FDA Fast Track drug candidate

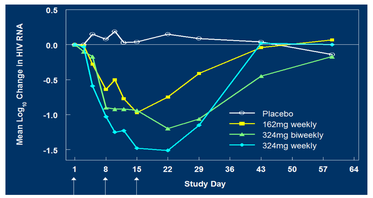

Figure 1. Antiviral Activity of Short-Term Monotherapy with PRO 140

Objectives

- The PRO 140_CD02 study was designed to evaluate efficacy, safety, and tolerability of PRO 140 in combination with an existing failing antiretroviral therapy (ART) regimen for one week followed by Optimized Background Therapy (OBT) for 24 weeks.
- The study population included treatment-experienced HIV-infected patients with CCR5-tropic virus with plasma HIV-1 RNA levels ≥ 400 copies/mL despite ongoing antiretroviral therapy with documented genotypic or phenotypic resistance to ART drugs within three drug classes (or within two drug classes with limited treatment options).
- The primary efficacy endpoint for this study was proportion of participants with a 0.5 $\log_{10}$ or greater reduction in plasma HIV-1 RNA viral load from baseline at the end of the 1-week double-blind treatment period.

Enrollment

Key Inclusion Criteria for CD02 study:

- age ≥18 years
- Exclusive R5-tropic virus (HIV-1 Trofile™ Assay)
- Plasma HIV-1 RNA ≥ 400 copies/mL at Screening
- Treatment-experienced with documented resistance to at least one ART drug within three drug classes or within two drug classes and have limited treatment option.

Key Exclusion Criteria for CD02 study:

- CXCR4-tropic virus or Dual/Mixed tropic (R5X4) virus
- Any active infection or malignancy requiring acute therapy
- No viable treatment options
- ≥ Grade 3 DAIDS lab abnormality
- Any vaccination within two weeks prior to the first study dose

Study Design

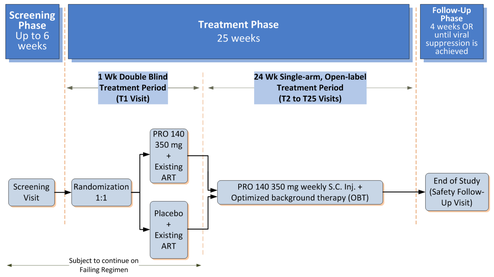

Figure 2. Study Design Schematic

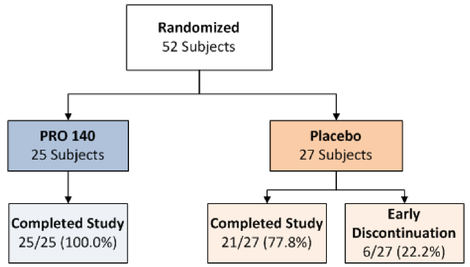

Figure 3. Subject Enrollment

Baseline Characteristics

Summary of Baseline Characteristics

Parameter	Characteristic	PRO 140 N=25	Placebo N=27	Total N=52
Time since HIV Diagnosis (Years)	Median	19.0	22.0	21.5
	Min - Max	4.0-34.0	4.0-37.0	4.0-37.0
Peak Viral Load (copies/mL)	>100000, n (%)	6 (24.0)	12 (44.4)	18 (34.6)
Baseline Viral Load (copies/mL)	Mean (SD)	24024(52562)	18400(24850)	21104(40287)
	Min - Max	23.0-253050	0.0-79224	0.0-253050
Baseline CD4+ Cell Count	Mean (SD)	319.1(197.3)	278.1(242.8)	297.8(220.9)
	Min - Max	16.0-735.0	4.0-1133.0	4.0-1133.0
Number of ART Drug Exposure Prior to Enrollment	Mean (SD)	11.8 (4.8)	9.6 (4.2)	10.7 (4.6)
	Min - Max	6.0-24.0	3.0-19.0	3.0-24.0
Number of ART Drug with Documented Resistance	Mean (SD)	9.4 (5.8)	8.8 (3.3)	9.1 (4.6)
	Min - Max	0.0-24.0	5.0-15.0	0.0-24.0
Approximated Months On Baseline ART (Failing) Regimen	Mean (SD)	24.9 (30.2)	33.6 (47.2)	29.4 (39.8)
	Min - Max	2.0-120.0	4.0-252.0	2.0-252.0
Approximate VL Prior Initiation Of Baseline ART (Failing) Regimen	Mean (SD)	32770.4 (40019.3)	79181.8 (146405.1)	56904.3 (110617.8)
	Min - Max	30.0-140000.0	100.0-600000.0	30.0-600000.0

Table 1. Summary of Baseline Characteristics

- Mean Age: 52.4 years
- 73.1% Male
- 51.9% Caucasian
- Enrolled subjects were exposed to an average of 11 ART drugs, excluding booster drugs. These enrolled subjects had documented resistance to an average of nine ART drugs with a reported maximum of 25 ART drugs, excluding partial sensitivity or decreased susceptibility.

Primary Efficacy Endpoint

Subjects with 0.5 $\log_{10}$ or Greater Reduction
in HIV-1 RNA viral load from baseline at the end of the 1-week double-blind treatment period

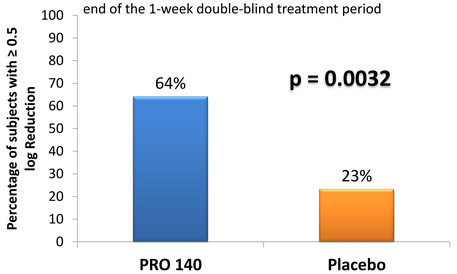

Figure 1. Percentage of patients with >0.5 reduction in plasma HIV-1 RNA copies/mL

Additional Key Endpoints

Table 2: Mean Change from Baseline in CD4+ Cell Count at Week 25

Visit	Statistic	Result	Increase from Baseline [1]
Baseline	n	52	
	Mean (SD)	297.8(220.9)	
	Median	247.5	
	Min - Max	4.0 - 1133.0	
Week 25	n	42	42
	Mean (SD)	414.0(275.7)	85.9(175.2)
	Median	368.5	66.0
	Min - Max	29.0 - 1519.0	-312 - 784.0

[1] Change from baseline is based on patients with paired values

Additional Key Endpoints

- After 25 weeks of treatment:
  - 81% of subjects with viral load < 50 copies/mL
  - 92% of subjects with viral load < 400 copies/mL
- Anti-PRO 140 antibodies were not detected
- Favorable PRO 140 PK profile that allows once-weekly dosing
- No change in co-receptor tropism at virologic rebound

Safety

Summary of Adverse Events (AEs)

Parameter	N = 52 n(%)
Subjects with ≥ 1 AE	34 (65.4)
Subjects with ≥ 1 Treatment Related [1] AE	10 (19.23)
Subjects with ≥ 1 Severe AE	6 (11.5)
Subjects with ≥ 1 Serious AE	8 (15.4)
Subjects with ≥ 1 Treatment Related [1] Serious AE	0 (0.0)
Deaths	0 (0.0)
Subjects with discontinuation due to AE	1 (1.9)
All AEs	175
All Treatment Emergent Related [1] AEs	35
All Severe AEs	15
All Serious AEs	16
All Treatment Related [1] Serious AEs	0
All AEs leading to Drug Discontinuation	1

Table 3. Summary of Adverse Events
n = Number of subjects (numerator for percentages, where applicable)
[1] Related = Probably, Possibly, Definitely related to the study treatment.

- PRO 140 was generally well tolerated.
- No drug-related SAEs were reported.
- The majority of injection site reactions were mild in intensity and considered to be self-resolving.

Conclusions

- Significant plasma HIV-1reduction for subjects treated with PRO 140, compared to placebo-treated subjects, was observed after a single SC injection.
  - Subjects with ≥ 0.5 $\log_{10}$ copies/mL reduction:
    - 64% in the PRO 140 treated group
    - 23% in the placebo group
- PRO 140 is a simple, long-acting, and potent anti-HIV-1 agent when combined with OBT in heavily treatment-experienced patients with multiple ARV class resistance.
- PRO 140 offers several potential advantages over existing therapies in terms of infrequent weekly dosing and limited drug-drug or food interactions.

Path Forward

- CytoDyn is anticipating a 2019 BLA submission for PRO 140 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.
- A roll-over study, PRO 140 CD02-Extension, extended access to PRO 140 treatment when, in the opinion of the treating physician, PRO 140 was required to form a viable suppressive regimen. Out of 52 patients, 40 subjects enrolled into the extension study.
- The **PRO 140_CD03 study** was designed to assess the clinical safety and treatment strategy of PRO 140 SC as a long-acting, single-agent, maintenance therapy in virally suppressed HIV-1 patients with CCR5-tropic HIV-1 receiving combination antiretroviral therapy. Three doses were tested: 350 mg, 525 mg, and 700 mg as weekly SC regimen.
  - 24.62% (48/195) of patients treated with 525 mg PRO 140 experienced virologic failure.
  - 18.55% (23/124) of patients treated with 700 mg PRO 140 experienced virologic failure.

  Note: Virologic failure was defined as two consecutive VL values of > 200 copies/mL.
  - PRO 140 could be a paradigm shift in the treatment of HIV as a single-agent maintenance therapy.
- CytoDyn plans to explore the ability of PRO 140 to treat patients in several oncology indications.
  - The **CD07_TNBC study** has been initiated to study PRO 140 in patients with CCR5-positive, locally advanced or metastatic triple-negative breast cancer (mTNBC).

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