PRO 140 Single-Agent Maintenance Therapy for HIV-1 Infection: A 2-Year Update

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Introduction

- PRO 140 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 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
- No dose-limiting toxicity in animals and generally well tolerated in clinical studies
- Potent, long-term antiviral activity in clinical studies
- Designated FDA Fast Track drug candidate

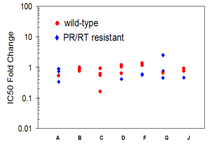


Figure 1. PRO 140 IC_{50} Fold Changes For HIV Subtypes

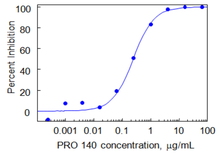


Figure 2. PRO 140 Concentration - Viral Inhibition Curve

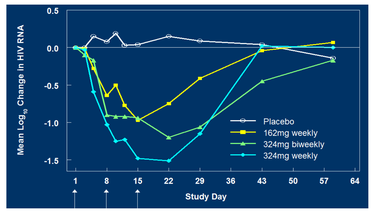


Figure 3. Antiviral Activity of Short-Term Monotherapy with PRO 140

Methods and Materials

- The Extension of CD01 study was designed to evaluate efficacy, safety, and tolerability of long-term PRO 140 monotherapy regimen (Weekly 350 mg SC injection) for the maintenance of viral suppression in subjects who were stable on effective combination ART
- Subjects were shifted from daily oral ART to weekly PRO 140 monotherapy for up to 12 weeks (with 1 week overlap of ART+PRO140) under CD01 study

Key Inclusion Criteria for CD01 study:

- age ≥18 years
- on stable ART regimen for 12 months and no change in last 4 wks prior to Screening
- Exclusive R5-tropic virus (Trofile™ DNA Assay)
- Plasma HIV-1 RNA <100 c/mL at Screening and no documented detectable viral loads (<50 c/mL) within the last 12 months prior to Screening
- Nadir CD4 count >200 cells/mm^3
- CD4 count >350 cells/mm^3 at Screening

Key Exclusion Criteria for CD01 study:

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

- Subjects who maintained viral suppression for 12 weeks were allowed to continue PRO 140 monotherapy for up to an additional 160 wks (3 yrs)

Study Design Schematic

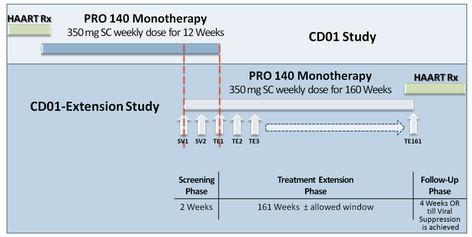


Figure 4. Study Design Schematic

Study Subject Disposition

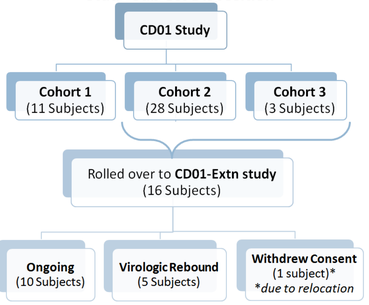


Figure 5. Study Subject Disposition

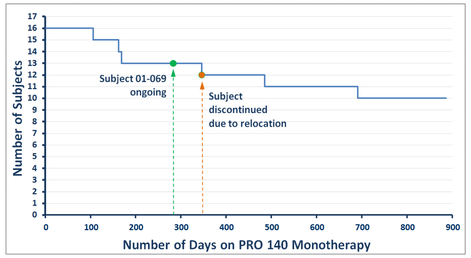
Results

Baseline Characteristics

Characteristic	Statistic	N = 16
Age (years)	Median	54.9
	Min - Max	26-68
Time since HIV Diagnosis (yrs)	Median	12.5
	Min - Max	2-37
Baseline CD4 cell count	Median	593
	Min - Max	365-1059
Gender	Male, n (%)	14 (87.5)
Race	Non-Caucasian, n (%)	3 (18.8)
Ethnicity	Hispanic or Latino, n (%)	4 (25.0)

N = number of eligible subjects within the population and the denominator for percentages
n = number of subjects within the group and the numerator for percentages

Time to Loss of Virologic Response



Graph 1. Kaplan-Meier Plot of Time to loss of Virologic Response

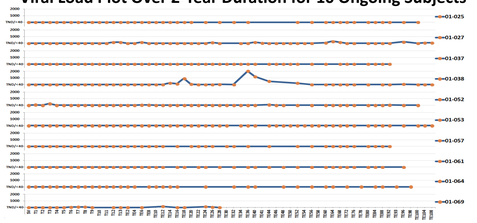
PRO 140 SC provides Long-term, Virologic Suppression in HIV infected Patients

Single Copy HIV-1 RNA Results

	Current Status	At the time of Abstract Submission		
Subject ID	Number of Weeks on PRO 140 monotherapy	Number of Weeks on PRO 140 monotherapy	Standard HIV-1 RNA Assay (Abbott RealTime) [LabCorp/Covance]	Single-Copy HIV-1 RNA Assay [bioMONTR Lab]
01-025	115	99	TND	**<1**
01-027	123	103	<40	**19**
01-037	105	91	TND	**<1**
01-038	121	103	TND	**<1**
01-052	115	99	<40	**10**
01-053	119	103	TND	**<1**
01-057	107	91	TND	**<1**
01-061	109	91	TND	**<1**
01-064	115	95	<40	**<1**
01-069	41	21	<40	**4**

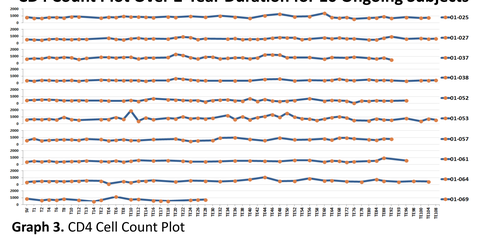
Single copy HIV-1 RNA results from ongoing subjects provides evidence of potent antiviral activity of PRO 140

Viral Load Plot Over 2-Year Duration for 10 Ongoing Subjects



Graph 2. Viral Load (HIV-1 RNA) Plot

CD4 Count Plot Over 2-Year Duration for 10 Ongoing Subjects



Graph 3. CD4 Cell Count Plot

CD4 cell counts maintained at stable levels throughout study

Additional Key Endpoints

- Anti-PRO 140 antibodies were not detected in any subject
- Favorable PRO 140 PK profile that allows once-weekly dosing
- No change in co-receptor tropism at virologic rebound

Safety Summary

- Generally well-tolerated
- No drug-related SAEs
- No discontinuation due to AEs
- No pattern of toxicity
- Administration-site reactions were infrequent, mild, transient, and self-resolving (in <10% of subjects)
- No dose-limiting toxicity in preclinical or clinical studies

Summary of Serious Adverse Events (SAEs)

Parameters	CD01 and CD01-Extn Study (N = 16)
Number of subjects with any reported SAE, n(%)	1 (6.3%)
Incidence of all SAEs	1
SAE, Preferred Term	Bile duct stone
Relationship to Study Drug	Unrelated

Summary of all AEs by Severity

Severity Grading	CD01 and CD01-Extn Study (N = 16)	
	Events	n (%)
Total	122	16 (100%)
Mild	94	7 (43.8%)
Moderate	25	9 (56.3%)
Severe*	0	0 (0.0%)

Note: Severity grading assessment missing for three AEs in the CD01-Extn study
*Severe AEs are those adverse events that were considered severe or life-threatening or causing death.

Summary of all AEs by Relationship to Study Treatment

Relationship to Study Drug	CD01 and CD01-Extn Study (N = 16)	
	Events	n (%)
Total	122	16 (100%)
Definitely Related	2	1 (6.3%)
Probably Related	2	2 (12.5%)
Possibly Related	8	5 (31.3%)
Unlikely	43	5 (31.3%)
Unrelated	65	3 (18.8%)

Note: Relationship to Study Drug assessment missing for two AEs in the CD01-Extension study
N = number of eligible subjects within the population and the denominator for percentages
n = number of subjects within the group and the numerator for percentages

Conclusions and Path Forward

- **PRO 140 CD01-Extension Phase 2b Study**
  - Weekly PRO 140 SC 350 mg was well tolerated and suppressed HIV-1 RNA levels below 40 copies/mL
    - For >40 weeks: in **81.3%** (13/16) of subjects
    - For >2 years: in **62.5%** (10/16) of subjects
  - These results support further development of PRO 140 as a simple, long-acting, single-agent maintenance therapy in selected HIV-1 patients who are experiencing antiretroviral toxicity, intolerance or suboptimal adherence to a daily oral combination regimen.
  - We are currently identifying factors that may predict PRO 140 treatment success.
- **Two Other Phase 2b/3 studies are ongoing:**
  - **Monotherapy Study** (PRO140_CD03): 300 subjects
    PRO 140 as long-acting, single-agent maintenance therapy for 48 weeks in virologically suppressed subjects with CCR5-tropic HIV-1 infection
  - **Pivotal Combination Study** (PRO140_CD02): 30 subjects
    PRO 140 in combination with other antiretroviral agents, in treatment-experienced adult patients infected with CCR5-tropic virus who have documented multi-antiretroviral class resistance and evidence of HIV-1 replication despite ongoing antiretroviral therapy

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