

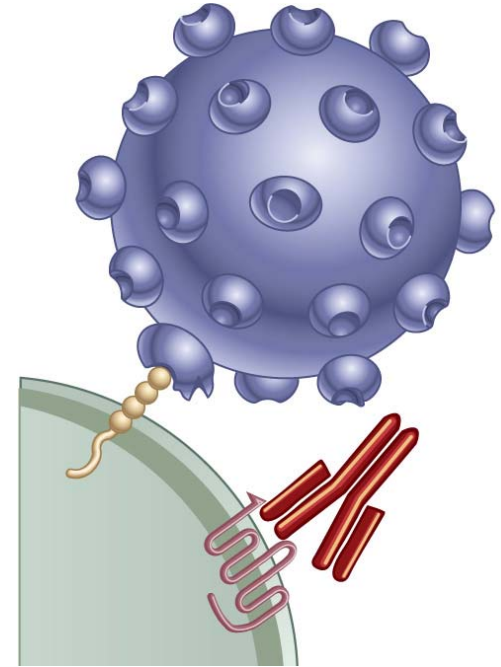
# Antiviral Activity and Tolerability of PRO 140, a Humanized Monoclonal Antibody to CCR5

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# PRO 140 Background

- Humanized monoclonal antibody targeting CCR5 co-receptor
- Broadly and potently inhibits R5 HIV-1 replication
- Distinct class of CCR5 inhibitor
  - Binds distinct extracellular domains
  - Competitive inhibition of HIV to binding site
  - Maintain natural activity of CCR5 *in vitro*
  - *In vitro* interactions with small-molecule CCR5 antagonists
    - Synergy
    - Limited cross-resistance
- Potential advantages
  - Low likelihood of drug-drug or drug-food interactions
  - Longer biological half life may allow for infrequent dosing
  - High barrier to resistance *in vitro*



# PRO 140 2301 and PRO 140 2101 Study Designs

<i>Objectives:</i>	Examine the tolerability, antiviral activity and PK of single IV doses (2301) or up to three SC doses (2101) of PRO 140 in HIV-infected subjects
<i>Design:</i>	Randomized, double-blind, placebo-controlled
<i>Eligibility:</i>	HIV-1 RNA $\geq$ 5000 copies/mL; R5 virus only CD4 $\geq$ 300 cells/ $\mu$ L, nadir $\geq$ 250 cells/ $\mu$ L No AIDS-defining illness No antiretroviral therapy within 12 weeks
<i>2301 Dose Groups:</i>	Placebo, PRO 140 5 mg/kg, PRO 140 10 mg/kg
<i>2101 Dose Groups:</i>	Placebo, PRO 140 162mg qweeklyx3, PRO 140 324mg q2weeksx2, PRO 140 324mg qweeklyx3
<i>Follow-up:</i>	58 days

# PRO 140 Studies 2301 and 2101

- Virological/immunological
  - Plasma HIV-1 RNA
  - Co-receptor tropism
  - PRO 140 susceptibility
  - CD4<sup>+</sup> T cells
- Safety
  - Physical examinations, vital signs, ECG
  - Adverse events
  - Laboratory tests (hematology, serum biochemistry, urinalysis)
- PK/PD
  - Serum PRO 140
  - Serum anti-PRO 140 antibodies
  - CCR5 lymphocytes

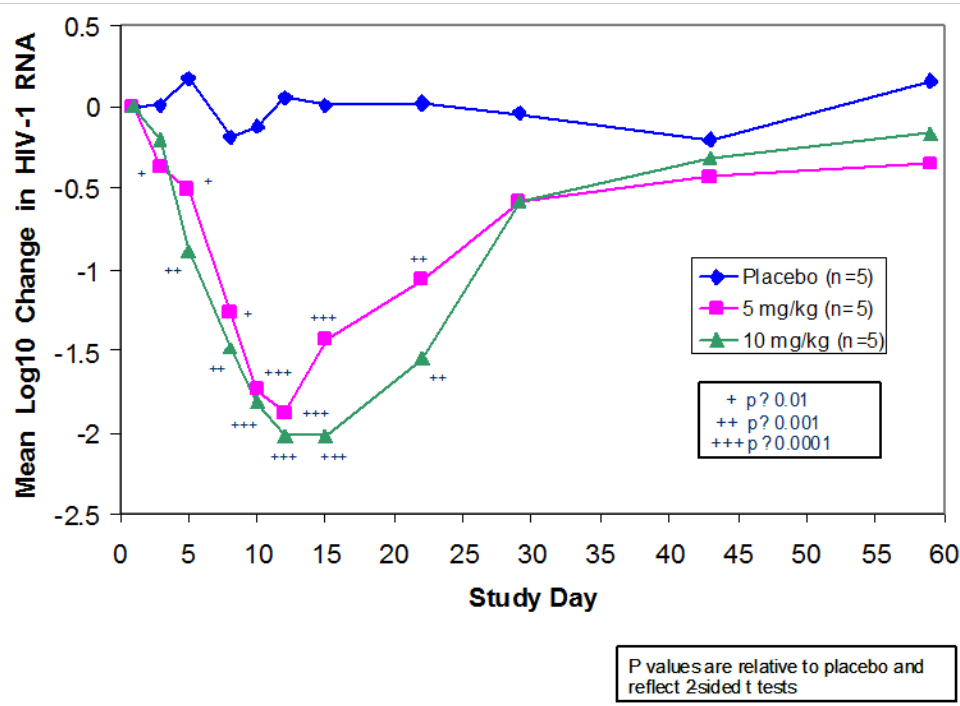
# PRO 140 2301 Interim Analysis

## *Baseline characteristics*

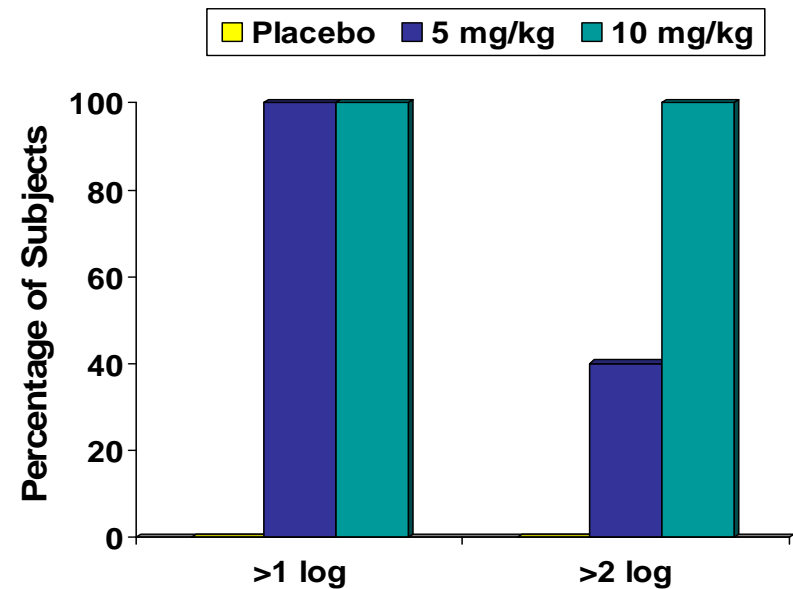
Characteristics	Placebo n=5	5 mg/kg n=5	10 mg/kg n=5
Age, median (range)	43.2 (39.1-56.6)	45.5 (28.0-51.8)	43.4 (25.9-57.2)
Gender (n), male/female	4/1	5/0	5/0
Race (n), black/white/other	0/5/0	0/5/0	1/3/1
Weight, kg median (range)	82.4 (73.3-92.7)	76.8 (63.5-126.0)	87.8 (67.5-95.0)
CD4, cells/ $\mu$ L median (range)	310 (264-549)	339 (267-475)	422 (255-797)
Log <sub>10</sub> HIV-1 RNA, copies/ mL median (range)	4.52 (4.27-4.95)	4.62 (3.88-4.75)	5.00 (3.79-5.31)

# PRO 140 2301 Interim Analysis

Mean change in viral load over time



Maximum reduction in HIV RNA



# PRO 140 2301 Interim Safety Analysis

System Organ Class Preferred Term	Placebo (N=5) n (%)	5 mg/kg (N=5) n (%)	10 mg/kg (N=5) n (%)
<b>Number of subjects with at least 1 adverse event</b>	<b>5 (100)</b>	<b>2 (40)</b>	<b>4 (80)</b>
<b>Eye disorders</b>	<b>3 (60)</b>	<b>0 (0)</b>	<b>0 (0)</b>
Lacrimation increased	1 (20)	0 (0)	0 (0)
Retinal Haemorrhage	1 (20)	0 (0)	0 (0)
Vision blurred	1 (20)	0 (0)	0 (0)
<b>Gastrointestinal disorders</b>	<b>1 (20)</b>	<b>1 (20)</b>	<b>1 (20)</b>
Anorectal Discomfort	0 (0)	0 (0)	1 (20)
Dental caries	1 (20)	0 (0)	0 (0)
Diarrhoea	0 (0)	1 (20)	0 (0)
Hemorrhoids	0 (0)	0 (0)	1 (20)
Nausea	0 (0)	1 (20)	0 (0)
<b>General disorders and administration site conditions</b>	<b>0 (0)</b>	<b>1 (20)</b>	<b>1 (20)</b>
Chest discomfort	0 (0)	0 (0)	1 (20)
Chills	0 (0)	0 (0)	1 (20)
Malaise	0 (0)	0 (0)	1 (20)

# Updated PRO 140 2301

- 31 subjects have been dosed – study completed
- 58 days of follow-up safety data available for all subjects
  - No serious adverse events reported
  - Aggregate group safety profile similar to interim safety profile
- Compilation and analysis of complete data sets under way

# Conclusions from PRO 140 2301

- High-level activity in subjects with R5 virus is consistent with previous findings
- Duration of antiviral effects increased with increasing dose
- No dose-limiting toxicity or safety issues

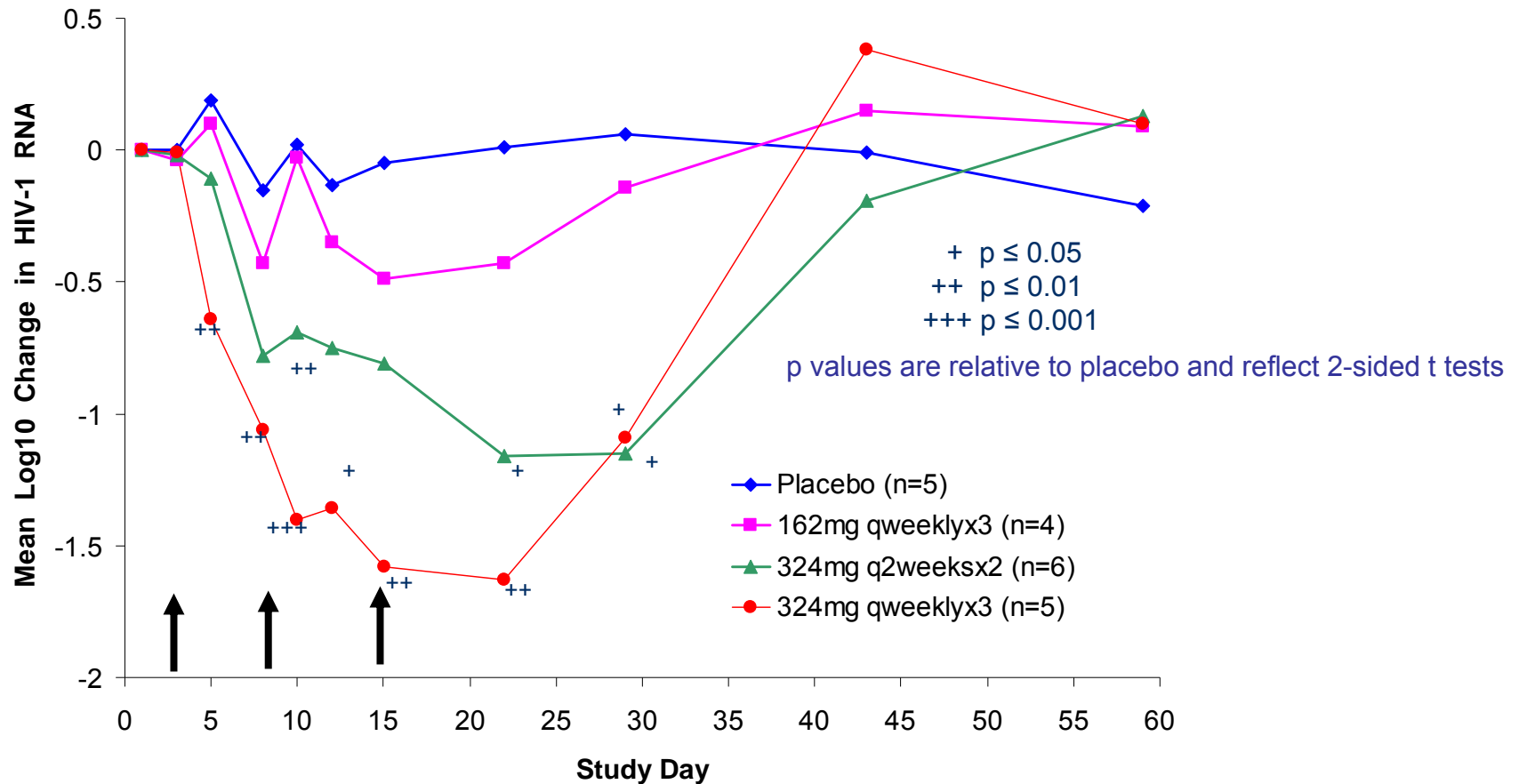
# PRO 140 2101 Interim Analysis

## *Baseline characteristics*

Characteristic	Placebo (n=5)	162mg weekly (n=4)	324mg biweekly (n=6)	324mg weekly (n=5)
Age, median (range)	34.9 (32.3-49.2)	40.4 (29.1-44.4)	44.5 (35.9-49.7)	41.1 (34.8-53.6)
Gender (n), male/female	4/1	4/0	5/1	5/0
Race (n), black/white/other	2/3/0	2/2/0	3/3/0	2/3/0
Weight, kg median (range)	78.6 (59.4-90.5)	82.4 (75.0-94.4)	91.5 (58.9-102)	68.2 (60.8-81.6)
CD4, cells/ $\mu$ L median (range)	411 (393-878)	320 (307-390)	504 (362-850)	389 (341-638)
Log <sub>10</sub> HIV-1 RNA, copies/mL median (range)	4.03 (3.94-5.13)	4.47 (4.18-4.67)	4.89 (4.03-5.12)	4.27 (3.61-4.54)

# PRO 140 2101 Interim Analysis

## Mean change in viral load over time



# PRO 140 2101 Interim Analysis

## *Safety*

- 162mg and 324mg SC doses of PRO 140 generally well tolerated
- Drug-related serious adverse events: None
- Drug-related adverse events leading to study discontinuation: None
  - One placebo subject discontinued due to the frequency of blood draws
- Dose-limiting toxicity: None
- Administration-site reactions
  - Minimal to mild
  - Transient and self-resolving
  - Similar in placebo and PRO 140 treatment groups

# Conclusions from PRO 140 2101

- PRO 140 SC demonstrated significant, rapid, dose-dependent and highly significant antiviral effects
- Duration of viral load suppression in SC administration sustained for >10 days following last dose
- Further viral load reductions seen with 324mg PRO 140 administered at weekly and biweekly intervals
- PRO 140 SC generally well tolerated

# Overall Conclusions

- Administration of PRO 140 via either SC or IV routes demonstrates reductions in viral load that were substantial from one to greater than three weeks
- Broad spectrum of exposure in early studies reveals no evidence for dose limiting toxicity
- Either IV or SC offer potential for infrequent dosing that may enhance compliance and clinical outcomes
- Use of approved devices that allow for self administration of SC PRO 140 anticipated in future trials

# Acknowledgments

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