

Antiviral Effects and Tolerability of the CCR5 Monoclonal Antibody PRO 140: A Proof of Concept Study in HIV- Infected Individuals

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for the PRO 140 1302 Study Team**

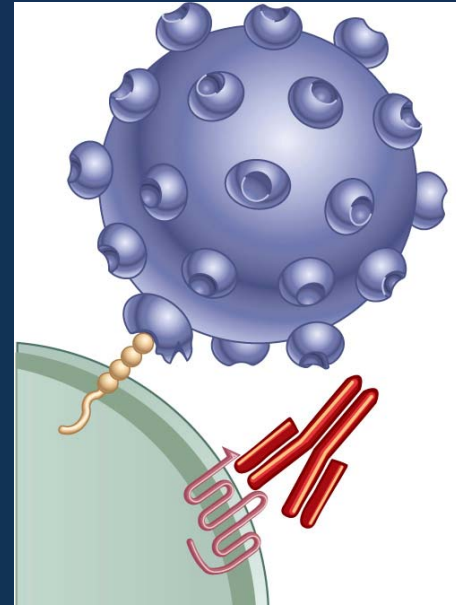
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This presentation is dedicated to the memory of Dr. Joseph Stavola.

PRO 140: Humanized CCR5 Monoclonal Antibody

- Broadly and potently inhibits wild-type and drug-resistant R5 HIV *in vitro*
- Distinct class of CCR5 inhibitor
 - Binds extracellular v. transmembrane site
 - Inhibits HIV via competitive v. allosteric mechanism
 - Inhibits HIV without blocking the natural activity of CCR5 *in vitro*
 - Inhibits HIV resistant to small-molecule CCR5 antagonists
 - Synergistic with small-molecule CCR5 antagonists
 - Potential for improved tolerability without drug-drug or food interactions
 - Potential for infrequent dosing
- Well tolerated in preclinical studies and in healthy volunteers
- Designated FDA Fast Track drug candidate



PRO 140 1302 Study

Design

- Objectives:* Examine the tolerability, antiviral activity and PK of single-dose intravenous PRO 140 in subjects with asymptomatic HIV infection
- Design:* Randomized, double-blind, placebo-controlled study
- Eligibility:* HIV-1 RNA > 5000 copies/mL; R5 virus only
CD4 > 250 cells/ μ L, nadir > 200 cells/ μ L
No AIDS-defining illness
No antiretroviral therapy for \geq 3 months
- # Subjects:* 39 (~10/group)
- Nominal Doses:* 0, 0.5, 2 & 5 mg/kg
- Follow-up:* 59 days

PRO 140 1302 Study

Evaluations

- Virological ✓
 - Plasma HIV-1 RNA
 - Co-receptor tropism
 - PRO 140 susceptibility
- Safety ✓
 - Physical examinations, vital signs, ECG
 - Adverse events
 - Laboratory tests (hematology, serum biochemistry, urinalysis)
- PK/PD ICAAC
 - Serum PRO 140
 - Serum anti-PRO 140 antibodies
 - CCR5 lymphocytes

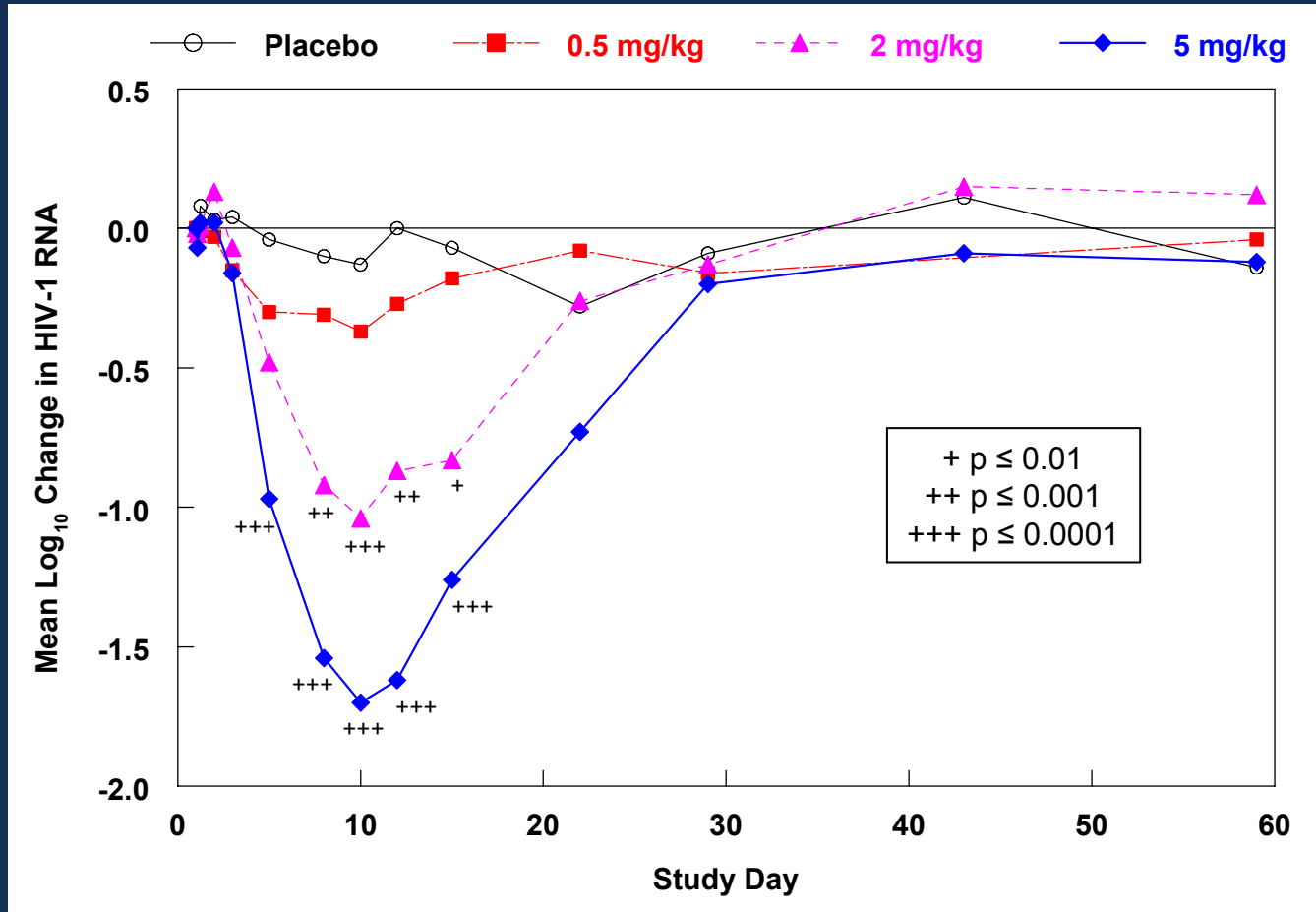
PRO 140 1302 Study

Subject baseline characteristics

Characteristic	Placebo (n=9)	0.5 mg/kg (n=10)	2 mg/kg (n=10)	5 mg/kg (n=10)	All Subjects (n=39)
Age, median (range)	40.3 (23-8-50.2)	37.1 (24.1-53.2)	37.6 (23.2-51.5)	42.8 (22.9-61.1)	40.3 (22.9-61.1)
Gender (n), male/female	8/1	10/0	8/2	5/5	31/8
Race (n), black/white/other	4/5/0	4/4/2	4/6/0	5/4/1	17/19/3
Weight, kg median (range)	81.4 (57.3-101.7)	81.0 (54.2-111.4)	81.7 (55.9-142.9)	73.4 (52.7-86.8)	80.9 (52.7-142.9)
CD4, cells/ μ L median (range)	439 (281-555)	493 (443-762)	438 (269-613)	535 (303-853)	484 (269-853)
Log ₁₀ HIV-1 RNA, copies/mL median (range)	4.44 (3.98-5.61)	4.45 (3.79-5.54)	4.44 (3.89-4.94)	4.37 (3.81-5.36)	4.43 (3.79-5.61)

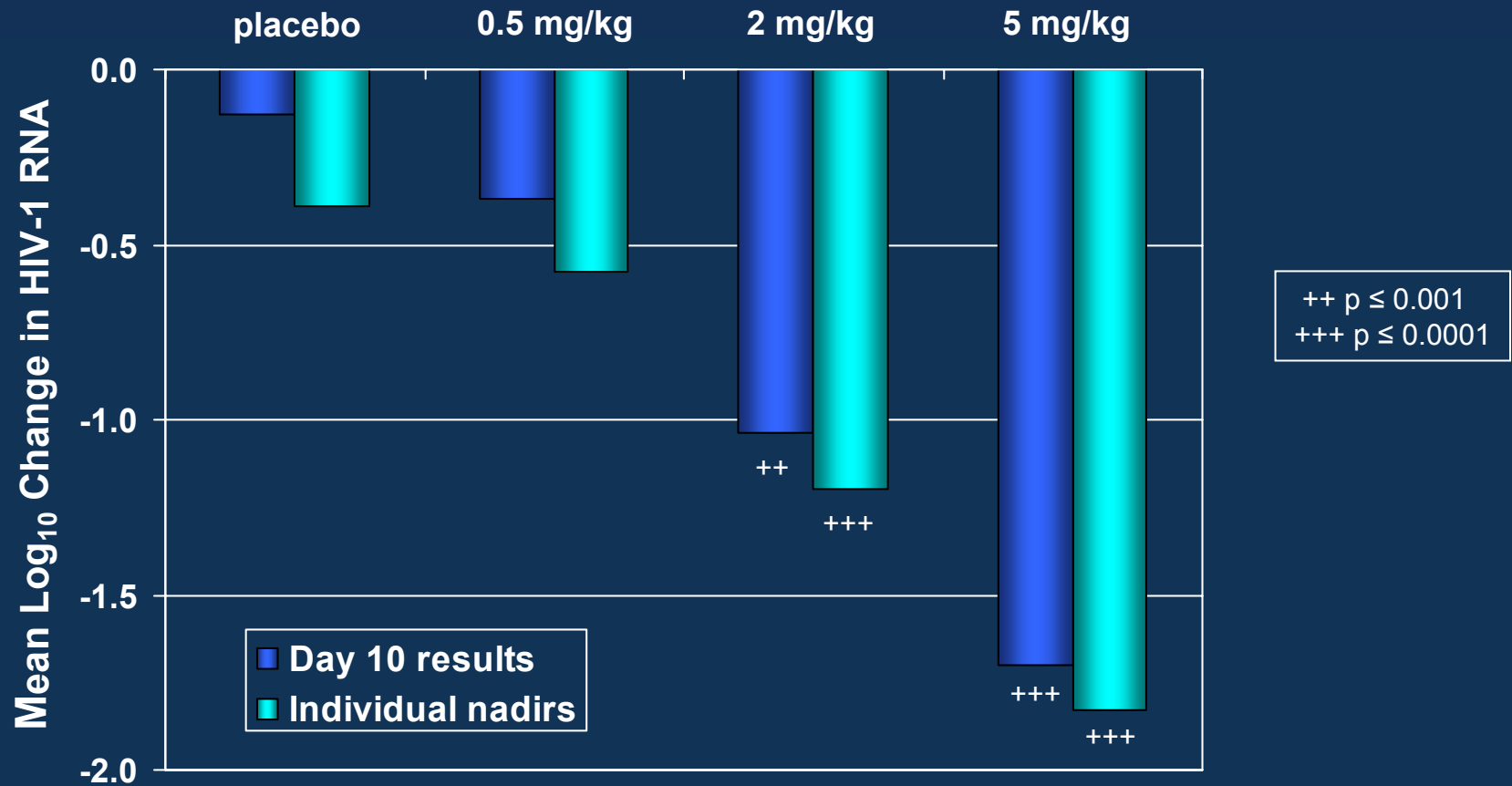
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Antiviral effects



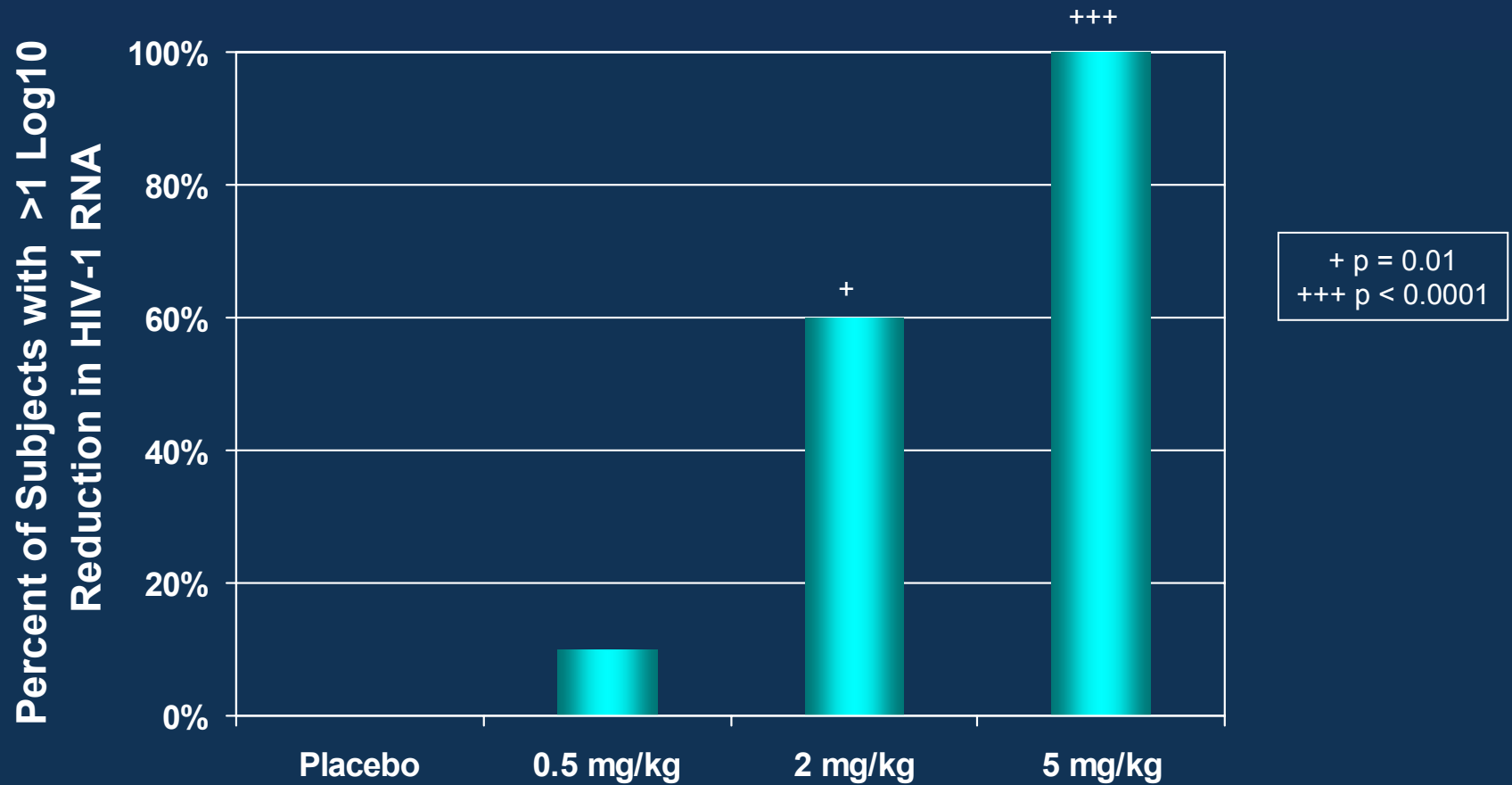
PRO 140 1302 Study

Antiviral effects



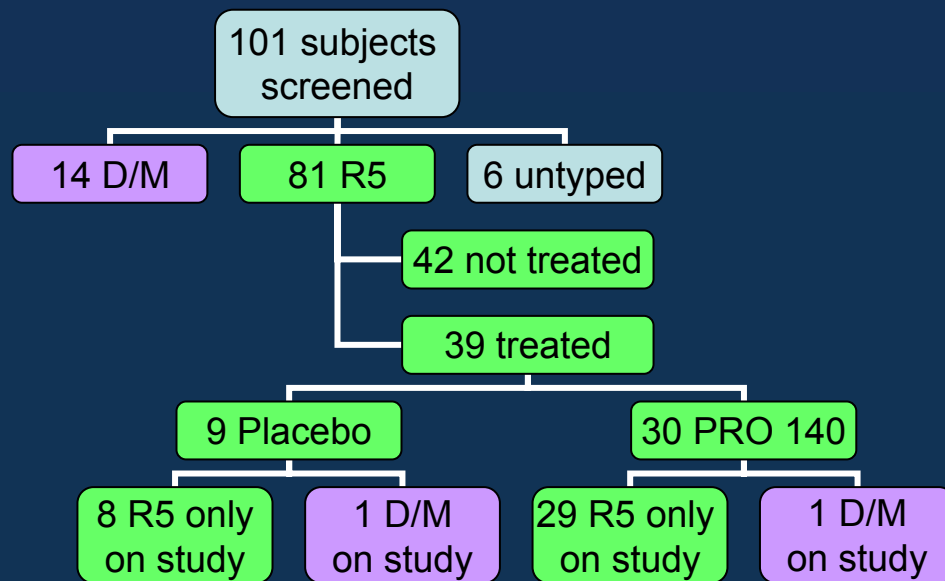
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Virological response rate



PRO 140 1302 Study

Co-receptor tropism results (*Trofile*TM, Monogram Biosciences)



- Dual/mixed (D/M) tropism assay results

- Placebo: 1/9 subjects (11%; Days 1, 8, 29 and 59)
- PRO 140 (0.5 mg/kg): 1/30 subjects (3%; Day 8 only)

- Clonal analysis of pre-dose and D/M viruses initiated

PRO 140 1302 Study

Safety

- No drug-related serious adverse events
- No dose-limiting toxicity
- No obvious pattern of toxicity
- No change in plasma RANTES (CCL5)
- Transient rise in CD4 lymphocytes at 5 mg/kg
 - 129 cells/mm³ (29%) average increase at Day 8 (p=0.055)
 - Levels remained elevated for 3 weeks post-treatment

PRO 140 1302 Study

Summary

- **Potent and prolonged antiviral activity**
 - Highest single-dose viral load reductions yet reported
 - 1.83 log₁₀ or 98.5% reduction on average
 - 2.5 log₁₀ or 99.7% individual reductions
 - Effects maximal on Day 10 and lasted for 2-3 weeks post-dose on average
 - Dose-dependent and highly significant
 - 100% response rate at top dose
- **Generally well tolerated**
 - No drug-related SAEs
 - No dose-limiting toxicity

PRO 140 Next Steps

- Complete PK/PD analyses and present findings at ICAAC
- Meet with FDA
- Initiate additional clinical studies later this year

Subcutaneous (SC) PRO 140

Feasibility of SC delivery

- Feasibility supported by:
 - Potent and prolonged antiviral activity
 - Favorable solubility
 - 6-month preclinical safety studies
 - Favorable bioavailability in preclinical models
- Weekly and q2weeks SC dosing predicted to provide desired PRO 140 drug levels
- Potential to provide the first long-acting self-administered therapy for HIV

Subcutaneous (SC) PRO 140

SC monoclonals establish precedence

	Fuzeon® Roche/Trimeris	Raptiva® Genentech	Enbrel® Amgen/Wyeth	Xolair® Genentech	Humira® Abbott	PRO 140 Progenics
basis of comparison	approved use	approved use	approved use	approved use	approved use	target profile
route	SC	SC	SC	SC	SC	SC
use	chronic	12 weeks	chronic	chronic	chronic	chronic
indication	HIV	psoriasis	RA & other	asthma	RA & other	R5 HIV
molecular class	HIV peptide	CD11a mAb	TNFR-Fc	IgE mAb	TNF mAb	CCR5 mAb
frequency	BID	1 week	1 week	2-4 weeks	2 weeks	~2 weeks
pH	9	6.2	6.3	<6	5.2	~ neutral
ISR warning, precaution or neither	warning	neither	neither	neither	neither	neither

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PRO 140 1302
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Study Team

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