



# PRO 140

First self-administered antibody therapy for HIV  
in late-stage clinical development

March 2018

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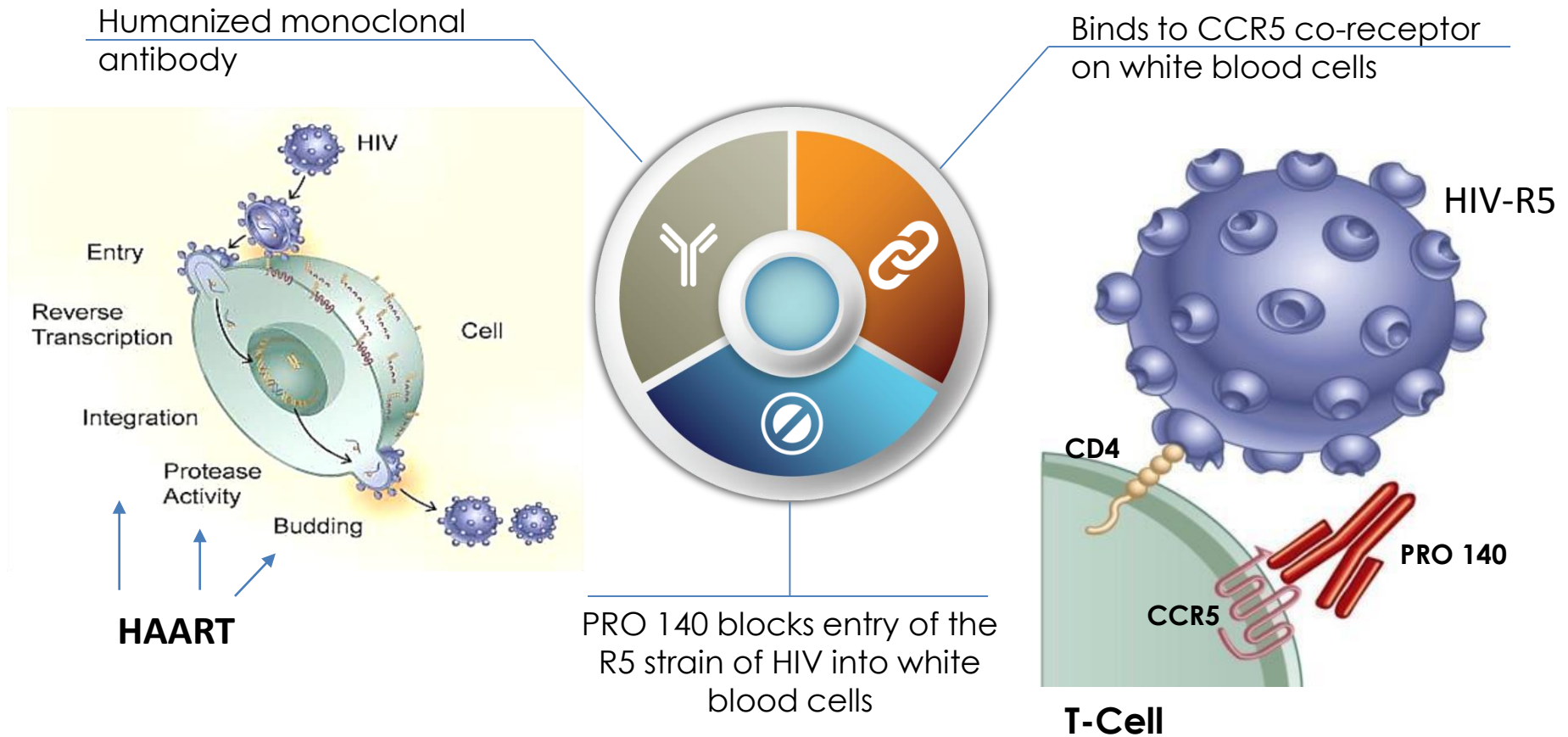
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- Large U.S. market (\$20 billion) for HIV therapies
- PRO 140 is currently under development for two different HIV indications:
  - **Combination with HAART** – primary endpoint achieved in February 2018
    - BLA filing in 2018, expected approval in 2019 with BTD
    - Potential market size is estimated at \$1 billion
  - **Monotherapy switch trial** – from HAART to single-drug therapy
    - Potential market size is estimated at \$4 billion
- Pipeline: Multiple opportunities in immunologic indications:
  - Transplantation, GvHD – Phase 2 clinical trial underway
  - Autoimmune disease & oncology – Positive data from preclinical studies
  - Other immunologic indications being explored

\*HAART - Highly Active Antiretroviral Therapy

## CCR5 is the Entry Receptor for R5 Strain of HIV



- Viral Load (VL) of an HIV patient = HIV particles per milliliter of the blood (copies/mL)
- A major goal of current therapy is to reduce transmission:
  - If  $VL < 50$  copies/mL, then transmission rate about zero

- Transmission of HIV remains high due to liabilities of HAART

- Major issues with current standard-of-care (HAART):

- Side effects
- Toxicity
- Resistance
- Compliance

Year	New HIV
2012	46,671
2013	46,770
2014	46,947
2015	47,092
2016	47,252
2017	47,420

- As a result, currently only about 35% of HIV patients in the U.S. have a suppressed viral load

# PRO 140 Advantages Over HAART



## PRO 140



## HAART

No serious side effects and no serious adverse events (SAEs) in >400 patients in 8 clinical trials

**Side Effects**

Ranges from mild to severe (Diarrhea, nausea, lethargy, depression)

Negligible toxicity

**Toxicity**

Problems with short- and long-term toxicity (hepatic toxicity, myelosuppression)

No drug resistance in patients on monotherapy for over 3 years

**Resistance**

76% of patients develop resistance

Weekly, easy, subcutaneous self administration

**Compliance**

Daily lifetime dosing with only 35% of patients with complete VL suppression

**PRO 140** may help reduce resistance to HAART and improve patient 'Quality of Life'

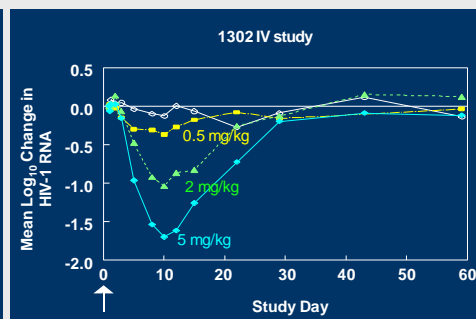
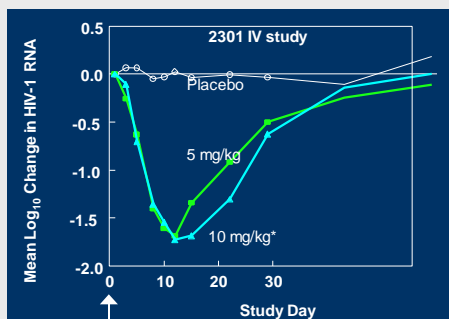
# PRO 140 Viral Load Reduction

## >400 HIV Patients (8 clinical trials)



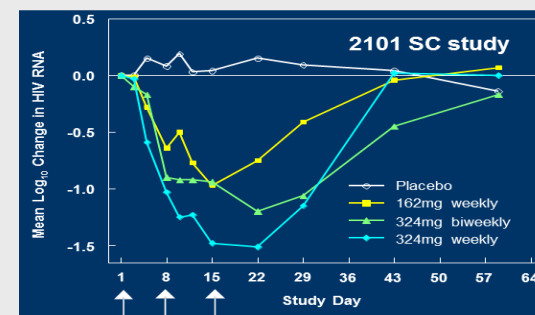
### Intravenous Administration

Significant single-dose viral load reductions over 3-week period



### Subcutaneous Administration

First proof of concept for a long-acting, self-administrable HIV drug administered weekly or bi-monthly



Mean Log<sub>10</sub> Change in HIV RNA

Study	Route	Treatment Groups	Reference
PRO 140 1302	IV	<ul style="list-style-type: none"> <li>Placebo (n=9)</li> <li>0.5 mg/kg single dose (n=10)</li> <li>2 mg/kg single dose (n=10)</li> <li>5 mg/kg single dose (n=10)</li> </ul>	Jacobson et al., J. Infect. Dis. 198:1345, 2008
PRO 140 2301	IV	<ul style="list-style-type: none"> <li>Placebo (n=11)</li> <li>5 mg/kg single dose (n=10)</li> <li>10 mg/kg single dose (n=10)</li> </ul>	Jacobson et al., AAC, 54:4137, 2010
PRO 140 2101	SC	<ul style="list-style-type: none"> <li>Placebo (n=10)</li> <li>162 mg Days 1, 8, 15 (n=11)</li> <li>324 mg Days 1, 15 (n=12)</li> <li>324 mg Days 1, 8, 15 (n=11)</li> </ul>	Jacobson et al., J. Inf. Dis. 201:1481, 2010

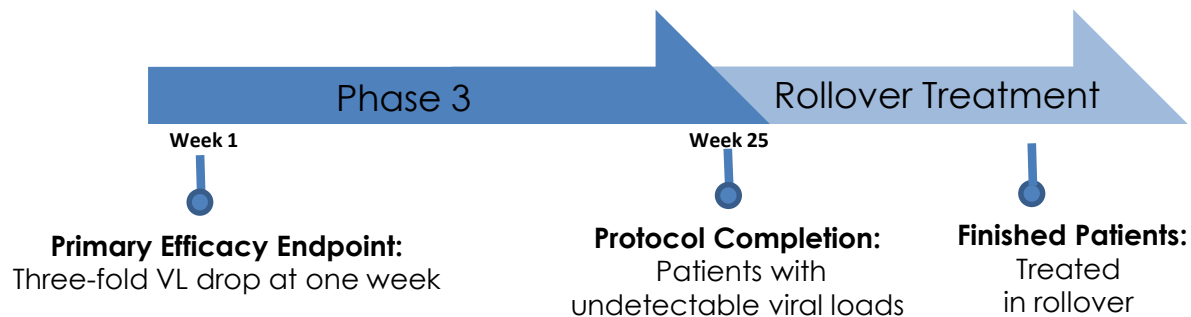
## Initial Approval and Label Expansion

Study	Design / Findings	Status
Phase 2b/3 Pivotal HIV Trial <b>Initial Approval</b>	<b>Combination Trial</b> Patients failing on HAART 1 week efficacy + 24 weeks safety	Primary endpoint achieved (p<0.01)
Phase 2b/3 Investigative HIV Trial <b>Label Expansion</b>	<b>Monotherapy Switch Trial</b> Long-term single agent therapy 48 weeks of monotherapy	Data in 2018



## Heavily Treatment-Experienced HIV-Infected Patients

- PRO 140 + HAART
- Path to 1<sup>st</sup> FDA approval of PRO 140
- Potential for Breakthrough Therapy Designation by FDA
- Patient enrollment completed
- Primary endpoint achieved and announced in February 2018



## HIV Patients Managed with HAART

- Long-term efficacy from CD01 Phase 2b study which has patients in a Monotherapy extension study for over 3 years

48 Weeks | N = 300



### Primary Endpoint:

Proportion of patients who remain on PRO 140 without experiencing virologic failure

### Secondary Endpoint:

Efficacy, safety and tolerability data

Safety results to support BLA submission for PRO 140 in combination with HAART

### Primary Objective:

Identify PRO 140 responders and achieve responder rate **above 70%**

### Secondary Objective:

Non-responders can resume their original HAART therapy without resistance

## Four Classes of Drugs Interference with HIV Life Cycle Inside of T-cells

## Entry Inhibitors

**NRTI**

**NNRTI**

**INTI**

**PI**

**EI**

**AZT**

**NVP**

**RTG**

**SQV**

Maraviroc

**ddl**

**DLV**

**EVG**

**RTV**

Ibalizumab

**ddC**

**EFV**

**DTG**

**IDV**

**PRO 140**

**d4T**

**ETV**

**NFV**

**APV**

**3TC**

**LPV/r**

**ABC**

**FPV**

**TDF**

**ATV**

**FTC**

**TPV**

**DRV**

HAART

3 Drugs from  
2 Different  
Classes

## Most Commonly Prescribed HAART Drugs

STR (Single Tablet Regimen)	<ul style="list-style-type: none"> <li>• Atripla      <b>Triumeq*</b></li> <li>• Stribild      <b>Quad*</b></li> <li>• Complera</li> </ul>
Nucleoside reverse transcriptase inhibitors (NRTI)	<ul style="list-style-type: none"> <li>• Truvada</li> <li>• Epzicom</li> <li>• Viread</li> </ul>
Non-Nucleoside reverse transcriptase inhibitors (NNRTI)	<ul style="list-style-type: none"> <li>• Sustiva</li> <li>• Intelence</li> <li>• Edurant</li> </ul>
Protease inhibitors (PI)	<ul style="list-style-type: none"> <li>• Prezista</li> <li>• Reyataz</li> <li>• Kaletra</li> </ul>
Integrase inhibitors (INI)	<ul style="list-style-type: none"> <li>• Isentress</li> <li>• Tivicay</li> </ul>

Source: GlobalData, based on primary research interviews and surveys conducted with KOLs and high-prescribing physicians in the countries included in this report; *AIDSinfo*, 2014c; CDC, 2014c; DHHS, 2014

\*Recent

# Entry Inhibitors *versus* HAART Combinations in Daily Single Pill Formulations

Entry Inhibitors - Heavily Treatment-Experienced (HTE) Patients	
Dosing Schedule	Suppressed viral load
Maraviroc, oral, twice daily	39% at 96 weeks
Ibalizumab, IV, biweekly	43% at 24 weeks
<b>PRO 140 (Ieronlimab), SC self injection, weekly</b>	<b>ongoing trial *</b>

HAART-Viral Life Cycle Inhibitors First-line Treatment Patients	
Daily Single Pill	Suppressed viral load (48-week trial)
Combivir	73%
Atripla	82%
Complera	86%
Stribild	87%
Triumeq	88%

\*majority of patients have maintained viral suppression at end of trial

# Current HIV Status in U.S.

(Source: GlobalData)



Year	Number of HIV patients in US	HIV Patients using ART	New cases in US
2003	1,021,840	575,883	51,818
2004	1,030,428	580,723	52,076
2005	1,039,791	586,000	52,169
2006	1,049,343	591,383	52,360
2007	1,081,789	609,669	52,510
2008	1,102,634	621,416	46,724
2009	1,123,727	633,304	43,994
2010	1,145,461	645,553	46,428
2011	1,174,049	661,664	46,582
2012	1,195,885	673,970	46,671
2013	1,218,323	686,616	46,770
2014	1,242,667	700,335	46,947
2015	1,268,852	715,093	47,092
2016	1,295,157	729,917	47,252
2017	1,320,244	744,056	47,420
2018	1,343,633	757,237	47,651
<b>2019</b>	<b>1,365,882</b>	<b>769,776</b>	<b>47,907</b>
2020	1,388,425	782,481	48,144
2021	1,410,694	795,031	48,424
2022	1,433,380	807,816	48,716
2023	1,456,102	820,622	49,003

PRO 140  
market  
launch

## Initial approval **Combination Therapy**

### U.S. Market Potential

- HAART failures: ~ 70,000 pts with two or more drug class resistances
- 70,000 pts x 70% (R5-HIV strain) = 49,000 HIV pts R5 eligible
- 49,000 pts x \$24,000 (current market pricing) = ~ **\$1.2 billion**

## Label Expansion **Switch to Monotherapy Maintenance**

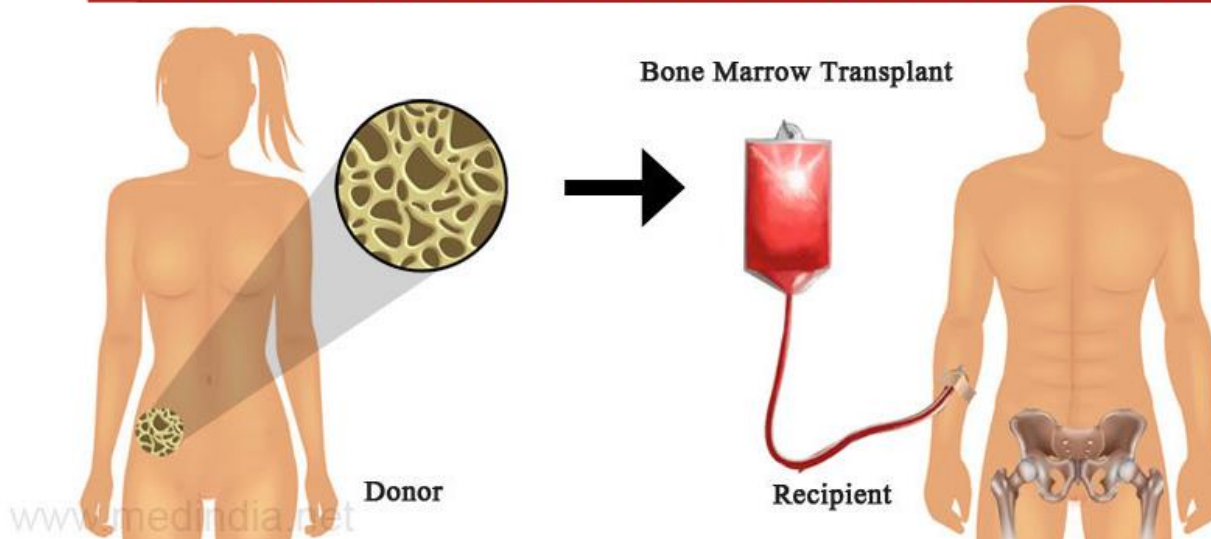
### U.S. Market Potential

- Target population (suppressed VL) = 17.5% of 1.3 million HIV+ = 227,500
- 227,500 pts x 70% (R5-HIV) = 159,250 pts
- 159,250 pts x \$24,000 (current market pricing) = ~ **\$3.8 billion**

- CCR5 – responsible for T-cell migration to sites of inflammation
- T-cell migration plays a crucial role in inflammatory responses
  - Transplantation rejection reactions
  - Autoimmunity
  - Chronic inflammation
  - Tumor metastases
- Transplantation reaction, GvHD, is the first immunologic indication for PRO 140
  - Phase 2 trial enrollment underway
  - 60 patients to be enrolled
  - 100-day trial period
  - Orphan Drug Designation granted by FDA



## BONE MARROW TRANSPLANT IS A MAJOR CAUSE OF GvHD.



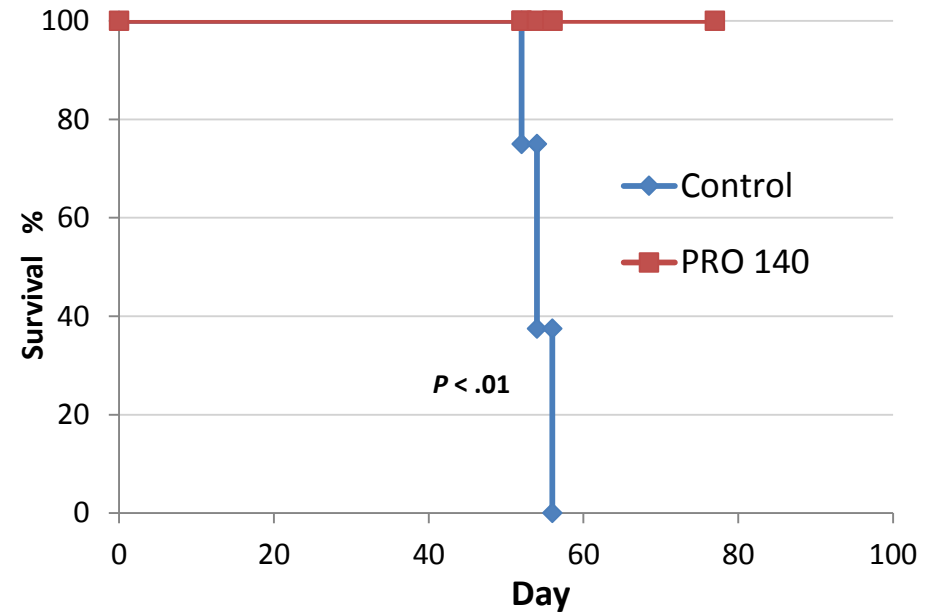
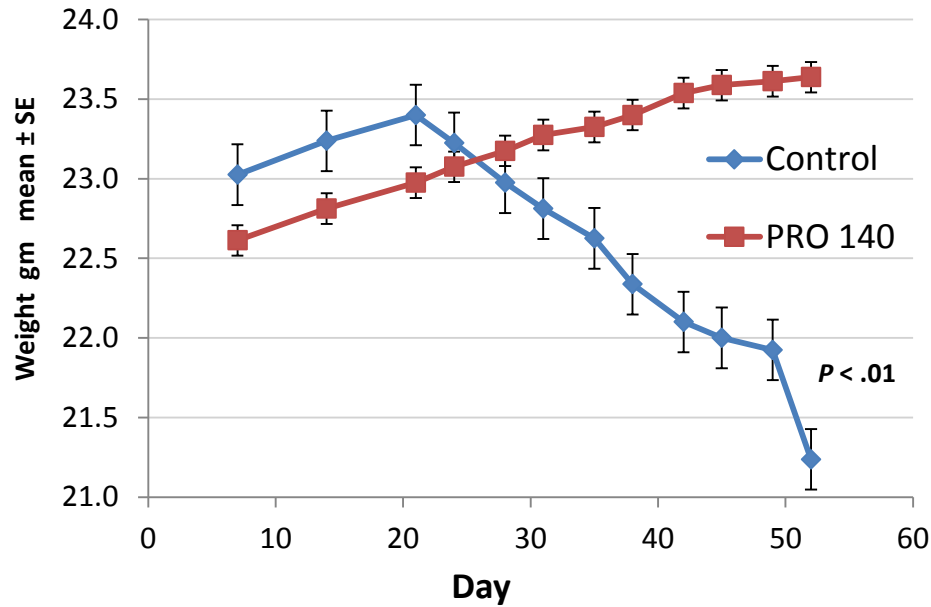
- Bone marrow transplant required due to aggressive cancer therapy
- GvHD occurs due to imperfect tissue match
- Mild: Cutaneous  
Severe: Liver & gut involvement

### Examples of Mild GvHD



# Effect of PRO 140 on Xeno-GvHD

## Human BM transplanted into immuno-deficient mice



## PRO 140 Important Milestones 2018/2019



Milestones	Target Dates
Phase 2b/3, Pivotal HIV Combination Trial Primary Endpoint	Completed
Medical Conference Presentations (CROI and ASM Microbe)	Completed
Published studies – GvHD (Preclinical study)	Completed
Orphan Drug Designation for GvHD	FDA Granted
Publication of Monotherapy (Phase 2b)	2Q2018
Publication Studies – HIV Combination Trial Primary Endpoint Study	2Q2018
Pivotal Phase 3 Endpoint Achieved (ASM Microbe late breaker)	June 2018
BLA Submission for HIV Combination Therapy	3Q2018
Phase 2b/3 Monotherapy Investigative Trial Readout	4Q2018
HIV Breakthrough Therapy Designation (BTD)	2018
HIV Combination Therapy Approval	2019w/BTD