Original Article

PRO 140, a monoclonal antibody targeting CCR5, as a long-acting, single-agent maintenance therapy for HIV-1 infection

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Background: PRO 140 is a humanized monoclonal antibody targeting CCR5 with potent antiviral activity in patients with CCR5-tropic HIV-1 infection. In phase 2b studies, we evaluated the long-term efficacy, safety, and tolerability of PRO 140 monotherapy in maintaining viral suppression for over 24 months in patients who were stable on combination antiretroviral therapy on entry into the trials.

Methods and Results: Forty-one adult patients, infected exclusively with CCR5-tropic HIV-1 with viral loads <50 copies/mL, were switched from daily oral combination ART regimens to weekly PRO 140 monotherapy for 12 weeks.Participants who completed 12 weeks of treatment without experiencing virologic rebound were allowed to self-administer PRO 140 as a 350 mg subcutaneous injection weekly, for up to an additional 160 weeks. Participants were monitored bi-weekly for one year, and every four weeks thereafter for virologic rebound.PRO 140 provided virologic suppression in 23/41 (56.1%) participants for 12 weeks and was well tolerated. Ten (10) participants are currently ongoing, of which nine participants have completed more than two years of monotherapy treatment (47–129 weeks). Participants experiencing virologic rebound achieved full viral suppression upon re-initiation of oral combination ART regimen. Anti-PRO 140 antibodies were not detected in any patient, and no drug-related major adverse events or treatment discontinuations were reported.

Conclusions: PRO 140 has a potential to address an unmet need for a long-acting, single-agent, maintenance regimen for HIV infection in selected patients. Studies are underway to determine host and/or virologic factors that may predict treatment success on PRO 140 monotherapy. Moreover, it has sufficient potency for a prolonged period of monotherapy that it would be an excellent component of a multi long-acting drug combination.

Keywords: PRO 140, monoclonal antibody, CCR5, monotherapy for HIV, HIV entry inhibitor, chemokine receptor, humanized antibody

Introduction

PRO 140 is a humanized IgG4, κ monoclonal antibody that blocks HIV-1 from entering and infecting immune cells by binding to the C–C chemokine receptor type 5 (CCR5) with high affinity.[1] PRO 140 inhibits entry by binding to the *N* terminus and the extracellular loop 2 domain of the CCR5 interfering with the final phase of viral binding to the cell surface prior to fusion of the viral and cell membranes.[2] This inhibition of viral entry does not interfere with the natural activity of CCR5 *in vitro*.[2–4]

PRO 140 inhibits genotypically diverse viruses, including wild-type, multi-drug-resistant HIV-1, viruses resistant to maraviroc, and both laboratory and low-passage clinical strains, and shows a high genetic barrier to viral resistance.[5–12] No dose-limiting toxicity has been observed in animal studies.[1]

Current human experience with PRO 140 consists of six completed clinical trials, which included 134 subjects exposed to PRO 140. Both single intravenous and multiple subcutaneous doses of PRO 140 have been well tolerated and have shown average reductions in plasma HIV-1 RNA levels of more than tenfold.[13–15] There has been no evidence of selection of drug resistant viruses or the X4 variant of HIV identified in prior PRO 140 clinical experience.[16–18] PRO 140 requires subcutaneous (SC) injection and its favorable pharmacokinetics allows for weekly dosing.[15]

In phase 2b studies, we evaluated the long-term efficacy, safety, and tolerability of PRO 140 monotherapy in maintaining viral suppression for over 24 months in patients who were stable on combination antiretroviral therapy on entry into the trials.

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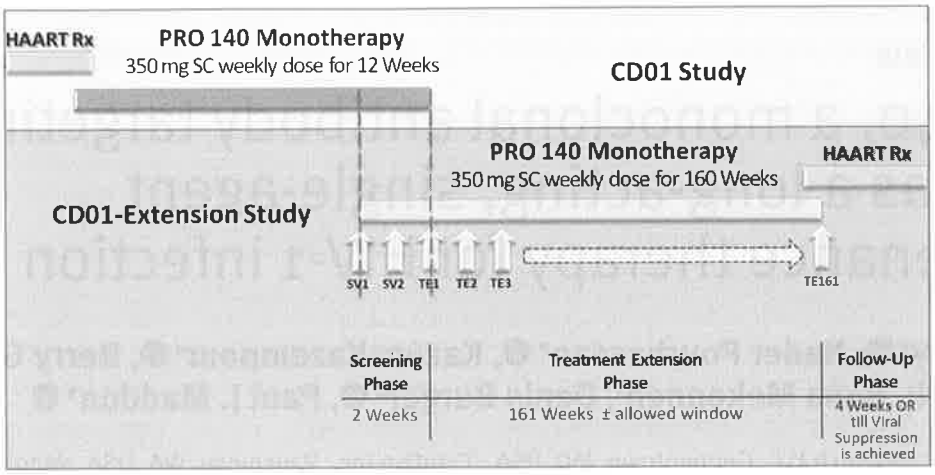

Figure 1 CD01 extension study design.

Methods

Ethics statement

These trials were approved by the Western Institutional Review Board® (WIRB) (WIRB Protocol Numbers: 20140327 and 20142157), and were registered on the ClinicalTrials.gov website (NCT02175680 and NCT02355184). The studies were conducted in line with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Guideline, and approved by the Institutional Review Board. All patients provided written informed consent prior to study participation.

Study design

The Phase 2b study (CD01) was designed to evaluate the efficacy, safety, and tolerability of PRO 140 monotherapy for the maintenance of viral suppression in participants who were stable on antiretroviral therapy (ART) (Figure 1). The study protocol required participants to have a plasma HIV-1 viral load less than 50 copies/mL, CD4 cell count greater than 350/mm^3, exclusive CCR5-tropic virus, on stable highly active ART (HAART) for 12 months with no change in regimen four weeks prior to screening, and no prior use of maraviroc. The median duration of prior ART regimen was five years. All enrolled subjects were on a combination of three or more ART drugs in which 17 had integrase inhibitors, 15 had NNRTI, and had protease inhibitors (nine boosted and two unboosted) as their third drug in the baseline ART regimen. These regimens were stopped at the start of treatment with PRO 140 monotherapy.

It is known that if viral rebound occurs while NNRTI levels are at sub-therapeutic levels (when HAART is stopped), NNRTI resistance may emerge. To avoid the possibility of viral rebound, there was a one week overlap of existing retroviral regimen and PRO 140 at the beginning of the study treatment built into the study to avoid the emergence of NNRTI resistance by "covering the NNRTI tail."

HIV-1 co-receptor tropism was evaluated at the screening visit using the Trofile® DNA Assay performed at Monogram Biosciences (South San Francisco, CA). Study participants were shifted from daily oral ART to 350 mg PRO 140 monotherapy for up to 12 weeks. PRO 140 was administered by a qualified medical professional or by self-administration. Subjects choosing to self-administer PRO 140 were trained by a licensed medical professional (MD, DO, PA, LPN, LVN, NP, or RN) at the site. The subject was then to self-administer PRO 140 under direction observation of the aforementioned site personnel. Subjects who were able to successfully self-administer the study treatment multiple times, per the site personnel's discretion at the clinic, were then given a supply of PRO 140 as well as a self-administration instruction sheet for the subsequent visits.

Study participants were monitored for viral rebound on a weekly basis following initiation of PRO 140 monotherapy and re-initiated their previous antiretroviral regimen if plasma HIV-1 RNA levels rose above 400 copies/mL on two consecutive blood draws at least three days apart.

Participants that experienced virologic rebound moved to the Follow-up Phase, restarted oral ART, and were monitored every four weeks for plasma HIV-1 RNA and CD4 T-cell count until viral load returned to less than 50 copies/mL. These participants were followed for up to 24–36 months after re-initiation of baseline ART to assess the durability of viral suppression after exposure to PRO 140 monotherapy.

The study initially enrolled 40 participants across two separate cohorts, with 12 participants enrolled under Cohort 1 and 28 participants enrolled in Cohort 2 after a DSMB evaluation of safety and efficacy data from Cohort 1. A third Cohort was added after the enrollment of 40 participants was completed (Figure 2). Sixty-eight (68)

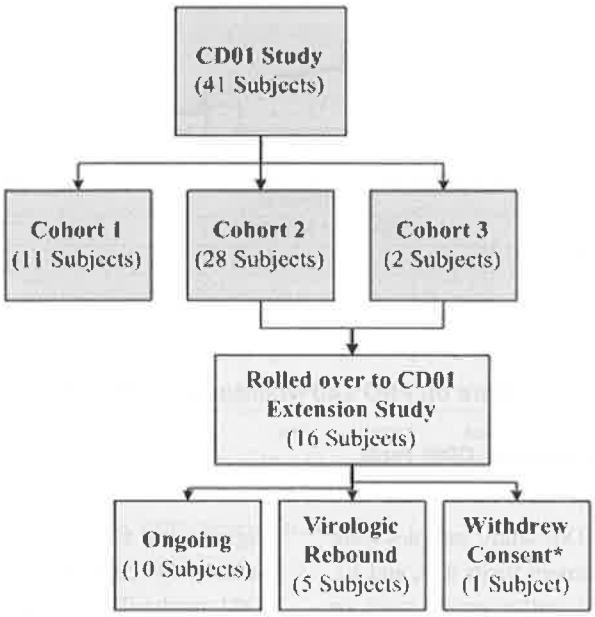

Figure 2 Study disposition, CD01 and CD01 extension studies.
Notes: *Withdrawal of consent due to relocation. (1) One enrolled patient in cohort 1 was considered not eligible since Trofile® DNA result was subsequently corrected to D/M at Screening Visit. (2) One enrolled patient in cohort 3 was considered not eligible since baseline Trofile® DNA result was reported as D/M at T1 (i.e. sample collected prior to first PRO 140 injection) Visit. Patient was enrolled based on screening Trofile® DNA result of CCR5 tropism.

patients were screened under Cohorts 1 and 2, with an additional 6 patients screened for Cohort 3.

Subjects in Cohorts 2 and 3 that completed 12 weeks of treatment under the CD01 protocol without experiencing virologic rebound could enter the Phase 2b Extension Study, which was designed to evaluate the long-term efficacy, safety, and tolerability of PRO 140 monotherapy for the maintenance of viral suppression. Eligible participants continued PRO 140 monotherapy for up to an additional 160 weeks under a study extension protocol (Figure 1).

Drug concentration was assessed through analysis of population PK. The blood samples for PK measurements were taken every four weeks starting from the baseline visit (prior to initiation of PRO 140 monotherapy). The blood samples were collected at the end of the dosage interval (trough level) i.e. prior to the subsequent PRO 140 dosing.

Efficacy analysis

This was an open-label study performed at a single center in San Francisco (CA), with eligible participants identified through referrals and site database. The primary efficacy endpoint of the CD01 and the CD01 extension studies was time to loss of virologic response after initiating PRO 140 monotherapy. Secondary endpoints evaluated the number of participants with virologic rebound at the end of the Treatment Phase, as well as mean change in viral load and CD4 cell count across the Treatment Phase.

Laboratory assessments

In the CD01 study, HIV-1 RNA was evaluated weekly using a quantitative assay (*Abbott Real Time*) with a lower limit of detection of 40 copies/mL. The CD4 cell count was assessed weekly for Cohort 1, and biweekly for Cohorts 2 and 3 using a TruCount Assay (LabCorp). In the CD01 Extension study, HIV-1 RNA and CD4 T-cell count (LabCorp) monitoring was done bi-weekly from weeks 12 to 52, then once every four weeks thereafter. Single-copy HIV RNA levels (bioMONTR Lab) were also evaluated at the two-year time point.

Cellular HIV DNA from all enrolled participants who experienced virologic rebound was tested for viral tropism phenotype using the PhenoSense® Entry Assay (Monogram Biosciences). HIV-1 RNA from plasma viral RNA obtained at the time of virologic rebound was used to construct envelope recombinant viruses. The ability of test compounds, AMD3100, maraviroc, and PRO 140, to block entry of recombinant viruses bearing these envelopes into CD4 T-cells expressing either the CCR5 or the CXCR4 receptor was assessed and compared to the concentrations required to block similar recombinant viruses constructed from pre-treatment cellular HIV DNA sequences in order to assess changes in 50 and 90% Inhibitory Concentrations (IC_{50} and IC_{90}) during the course of the study.

Participants were assessed for the development of anti-idiotypic antibodies and the pharmacokinetic properties

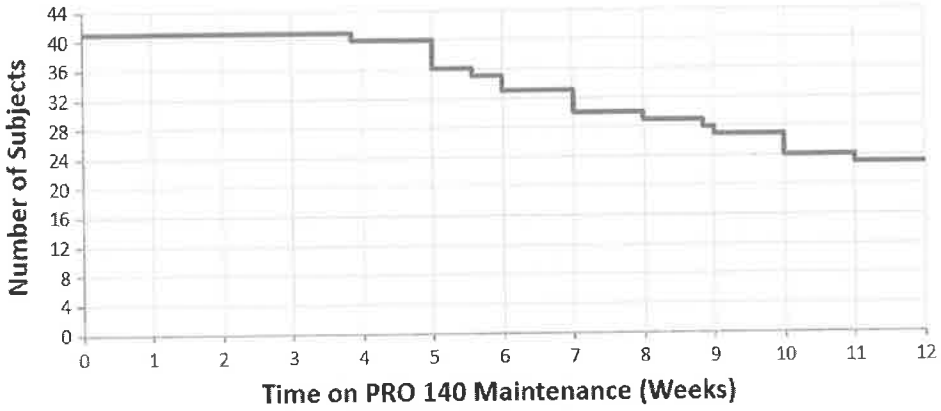

Figure 3 Time to loss of virologic response, CD01 study.

of PRO 140 (QPS, LLC). In the CD01 study, samples were taken at the Screening Visit, Treatment Visits 4, 8, and 12, and at virologic rebound, as well as the second week or fourth week of the Follow-up Phase. In the CD01 Extension study, all participants had laboratory samples collected at Screening Visit 1, at every fourth treatment visit, and if applicable at virologic rebound. There was no correlation between higher PRO 140 concentrations and adverse events.

Serum concentration of ART drugs was determined during the treatment phase in both studies to confirm adherence to the monotherapy regimen (Consolidated Laboratory Services, LLC).

Safety analysis

Safety was assessed by the evaluation of tolerability of repeated SC administration of PRO 140, as assessed by study participants (using Visual Analog Scale), investigator evaluation of injection site reactions, frequency of Grade 3 or 4 adverse events as defined by the DAIDS Adverse Event scale, and frequency of treatment–emergent serious adverse events.

Statistical methods

Data analyses were performed with SAS® software, version 9.3. All data collected from the two studies were presented as by-participant listings and also summarized according to the variable type. Summary statistics for continuous variables were presented using number of observations, mean, median, range, and standard deviation. Summary statistics for categorical variables were presented as frequency count and percentage. There were no pre-planned analyses of covariates and no imputation of missing data was performed.

Results

Population demographics and baseline characteristics

Forty-three (43) participants (Male/Female: 38/3) with median age of 55 years (26–72), median time since HIV diagnosis of 19 years (2–37) and median CD4 T-cell count of 609 cells/mm^3 (365–1240) were enrolled in the CD01 study. Two (2) patients were deemed ineligible for efficacy analysis post-enrollment due to presence of dual/mixed tropic virus in a blood sample collected at Screening/Baseline.

Sixteen (16) eligible participants, 14 male and two female, with a median age of 54.5 years (26–67) were enrolled in the CD01 Extension study. The majority of participants were Caucasian (81.3%). Participants had a median time since HIV diagnosis of 12.5 years (2–37) and median CD4 cell count of 593 cells/mm^3 (365–1059). In addition, the majority of subjects enrolled elected to self-administer PRO 140 in the extension protocol.

Efficacy analysis

In both studies, the primary efficacy endpoint was time to loss of virologic response after initiating PRO 140 monotherapy. Twenty-three (23) of 41 participants (56.1%) in the CD01 study maintained viral suppression throughout the 12 week monotherapy treatment phase. Seven (7) of these participants completed one week overlap of oral ART and PRO 140 at the end of Treatment Phase and moved into the Follow-up Phase, while the other sixteen (16) participants continued PRO 140 monotherapy in the ongoing CD01 Extension study.

Eighteen (18) subjects did not maintain viral suppression during the 12 week monotherapy treatment phase in the CD01 study (Figure 3). The mean time to virologic rebound was 51.3 days, ranging from 28 to 78 days. Participants who experienced virologic rebound moved to Follow-up Phase and restarted oral combination ART. Once ART was reinitiated, all 18 virologic rebound patients achieved viral suppression to less than 50 HIV-1 RNA copies/mL, with mean time to viral suppression of 46.6 days.

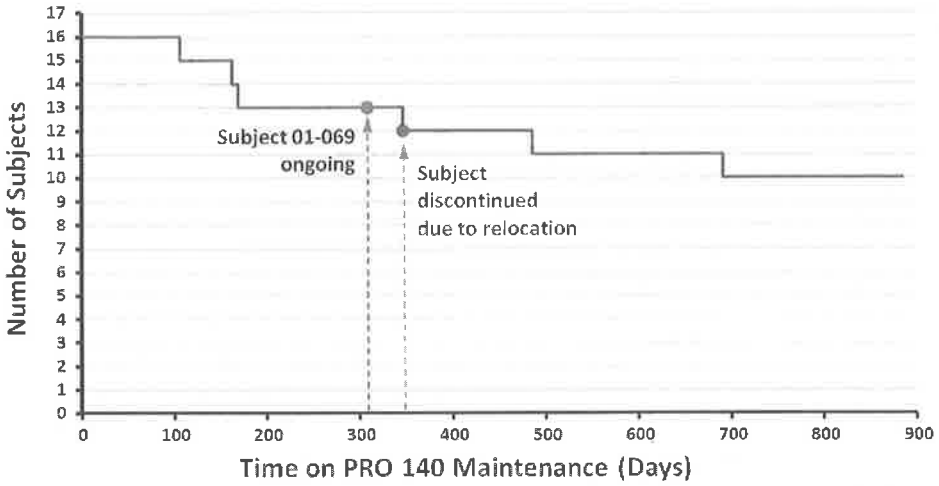

Figure 4 Time to loss of virologic response, CD01 extension study.

In the CD01 Extension study, 10 of the 16 participants remain in the study, of whom nine have completed over two years of treatment (Figure 4). One patient discontinued due to relocation after 49 weeks of virologic suppression and five participants experienced virologic rebound. The mean time to virologic rebound was 323 days. Participants unable to maintain viral suppression on PRO 140 monotherapy had their baseline ART regimen re-initiated, and all achieved complete viral suppression after ART re-initiation.

Participants experiencing virologic rebound were followed for up to 24 to 36 months after re-initiation of baseline ART and showed no long-term virologic or clinical consequences as a result of rebounding on PRO 140 monotherapy. The 10 participants currently ongoing in the CD01 Extension study have received PRO 140 monotherapy for time periods ranging from 47 to 129 weeks. Nine (9) of the 10 participants have completed more than two years of treatment with PRO 140 monotherapy. HIV-1 RNA levels remained suppressed below 40 copies/mL for 81% (13/16) of participants for greater than 40 weeks and greater than two years for 62.5% (10/16) of participants.

At the two-year time point, seven of the 10 study participants had viral loads of less than 1 copy/mL using single-copy HIV RNA assay (bioMONTR lab), while the other three had values of 4, 10, and 19 copies/mL.

In the CD01 Extension study, each patient demonstrated only CCR5-tropic HIV-1 virus at Screening, and no change in co-receptor tropism was reported when reassessed at virologic rebound.

Individual patient analysis of IC_{50} and IC_{90} values showed no significant changes in post-treatment values compared with pre-treatment baseline values for three test compounds, PRO 140, maraviroc, and AMD3100 in either the virologic rebound or non-virologic rebound groups. However, an aggregate analysis showed that the participants which experienced virologic rebound had higher IC_{90} values for PRO 140 at baseline (10.8 μg/mL) compared to participants without virologic rebound (6.7 μg/mL).

Anti-PRO 140 antibodies were not detected in any post-treatment sample from either study. The serum concentration (mean +/− SD) of PRO 140 at 4, 8, and 12 weeks of treatment was 18.2+/−8.5, 22.1+/−8.9, and 24.6+/−13.5 ug/mL, respectively. PRO 140 had a PK profile similar to that seen in prior clinical studies.

Safety analysis

Safety data were analyzed for 41 participants in the CD01 study and 16 participants in the CD01 Extension study (Table 1). One of 41 participants in the CD01 study experienced a serious adverse event (SAE), reported by MedDRA preferred term as transient ischemic attack, which was deemed not related to the study drug by the Principal Investigator. One of 16 participants in the CD01 Extension study experienced a SAE, reported by MedDRA preferred term as a bile duct stone, which was deemed not related to the study drug by the Principal Investigator.

In both studies, all definitely and probably treatment-related AEs were local injection site reactions and were mild, transient, and self-resolving. No other clinically relevant treatment-related effects were observed. The incidence of clinically notable abnormalities in vital signs, physical examination, and clinical laboratory tests was low.

Table 1 Summary of safety events, PRO 140_CD01 study, safety population

	CD01		CD01 Extension	
Category	*N* = 41		*N* = 16	
Preferred Term[1]	*n* (%)	Events	*n* (%)	Events
All SAEs	**1 (2.3)**	**1**	**1 (6.3)**	**1**
Transient ischemic attack	1 (2.3)	1	–	–
Bile duct stone	–	–	1 (6.3)	1
All definitely related AEs	**3 (7.0)**	**7**	**1 (6.3)**	**2**
Injection site pruritus	3 (7.0)	4	1 (6.3)	1
Injection site reaction	1 (2.3)	1	–	–
Injection site swelling	2 (4.7)	2	1 (6.3)	1
All probably related AEs	**4 (9.3)**	**4**	**2 (12.5)**	**2**
Administration site rash	1 (2.3)	1	–	–
Injection site pain	2 (4.7)	2	2 (12.5)	2
Injection site pruritus	1 (2.3)	1	–	–
All possibly related AEs	**7 (16.3)**	**14**	**5 (31.3)**	**8**
Diarrhea	2 (4.7)	2	1 (6.3)	2
Hypothyroidism	–	–	1 (6.3)	1
Vomiting	1 (2.3)	1	1 (6.3)	1
Fatigue	1 (2.3)	1	–	–
Pain	1 (2.3)	1	1 (6.3)	1
Upper respiratory tract infection	1 (2.3)	1	–	–
Back pain	1 (2.3)	2	–	–
Pain in extremity	1 (2.3)	1	–	–
Dizziness	1 (2.3)	1	1 (6.3)	1
Headache	2 (4.7)	2	1 (6.3)	1
Libido increased	1 (2.3)	1	–	–
Rash	1 (2.3)	1	1 (6.3)	1
All severe AEs[2]	**1 (2.3)**	**1**	–	–
Transient ischemic attack	1 (2.3)	1	–	–

[1]MedDRA Version 17.0.

[2]Severe AEs are those AEs considered severe, life-threatening, or causing death.

Notes: Relationship to study drug assessment is missing for two AEs in the CD01 Extension study.

All percentages are based on the number of participants in the Safety Population (*N*).

A participant is counted only once within each category, using the event with the maximum severity.

SAEs are those AEs that results in death, is life threatening (the subject is at immediate risk of dying from the AE), requires subject hospitalization or prolongs existing hospitalization, results in persistent or significant disability/incapacity and is a congenital anomaly/birth defectDefinitely related AEs are those AEs that the Investigator feels are incontrovertibly related to the study treatment.Probably related AEs are those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study treatment.Possibly related AEs are those AEs which, after careful medical consideration at the time they are evaluated, are judged unlikely but cannot be ruled out with certainty to the study treatment.

Discussion

Early efforts to use monoclonal antibodies to suppress HIV replication were largely unsuccessful, and despite nearly two decades of human studies, monoclonal antibodies have not found a significant role in HIV prevention or therapy. However, recent studies with broadly neutralizing antibodies targeting the V3 region of HIV gp120 envelope and the approval of ibalizumab for salvage patients have renewed interest into monoclonal antibodies as therapeutic agents.

The use of monoclonal antibodies targeting the HIV entry co-receptor, CCR5, provides a novel class of potential therapeutic agents. PRO 140 acts by binding CCR5 on hematopoietic cells and preventing viral entry whereas the current antiretroviral agents target viral replication targets in the HIV life cycle. Previous small molecule inhibitors of CCR5, vicriviroc and maraviroc, have shown inferior efficacy in phase 3 trials in both naïve and salvage patients compared to agents that interfere with the viral life cycle. These agents are allosteric inhibitors of HIV fusion with cell membranes and have agonist activity resulting in activation of downstream tyrosine kinases triggering off target side effects. In contrast, PRO 140 is a competitive inhibitor antagonist of HIV recognition of CCR5 with no agonist activation of tyrosine kinases. Current antiretroviral agents are used in combination regimens due to the rapid development of resistance associated with monotherapy with these agents. PRO 140 presents a high genetic barrier to resistance and its unique mechanism of action to block HIV-1 entry supports its use as monotherapy for HIV-1 infection. Additionally, PRO 140 offers several potential advantages over existing therapies in terms of infrequent weekly dosing, favorable tolerability, and limited drug–drug or –food interactions.

In the CD01 proof of concept PRO 140 monotherapy study, more than half of participants maintained viral suppression over the duration of 12 weeks, indicating the potential of PRO 140 to maintain viral suppression in a certain population of HIV patients. Virologic rebound patients achieved viral re-suppression after re-initiation of baseline ART regimen. Participants experiencing virologic rebound were followed for up to 36 months after re-initiation of baseline ART and showed no long-term virologic consequences as a result of PRO 140 monotherapy.

In the ongoing, proof of concept, long-term CD01 Extension study, 10 of the 16 eligible participants remain in the study, having received PRO 140 monotherapy for time periods ranging from 47 to 129 weeks. Sustained antiviral activity of PRO 140 was demonstrated with HIV-1 RNA levels continually suppressed for greater than two years for 62.5% (10/16) of participants. It should be pointed out that on an intent-to-treat basis, which includes both studies, the percent of patients without viral rebound would only be 33% (10/30). The single copy HIV-1 RNA assay showed viral suppression of less than 1 copy/mL in 70% (7/10) of participants at the two-year time point. With improved patient selection to identify potentially

responding patients, further development of PRO 140 as a simplified maintenance monotherapy regimen for HIV-1 infection could be justified.

Overall, PRO 140 was well tolerated with no related SAEs or discontinuation due to AEs observed in these studies. Other potential benefits of PRO 140 monotherapy include reductions in ART non-adherence and toxicity, along with reduction in other complaints related to intolerance of combination ART regimens.

Given the limited sensitivity and specificity of the Trofile® DNA Assay, it was not unexpected that two participants were reported as having dual/mixed (D/M) tropism at the time of virologic rebound using the standard Trofile® RNA Assay. The emergence of CXCR4-tropic virus was likely due to pre-existing CXCR4-tropic viruses rather than true co-receptor "switching," as no phenotypic shift in the IC_{50} and IC_{90} concentration was observed.

There was no significant change in viral susceptibility to PRO 140 in virologic rebound and non-virologic rebound groups of patients assessed by post-treatment IC_{50}, and IC_{90} values when compared with pretreatment baseline values. This indicates that the ligand-receptor recognition profile of the CCR5 co-receptor was not altered during the course of the study. In addition, no changes in HIV-1 co-receptor tropism following virologic rebound were seen. PhenoSense® Entry results for PRO 140, maraviroc, and AMD3100 showed no significant change in post-treatment IC_{50}, and IC_{90}, compared with baseline results in virologic rebound patients. However, there was a noted difference in the IC90 values from virologic rebound (10.8+/−9.28) and non virologic rebound (6.7+/−6.8) groups on entry analysis indicating that more PRO 140 was required to reach IC90 by the group that was destined to rebound on PRO 140 monotherapy.

In the absence of evidence of emergence of viral isolates with reduced susceptibility to PRO 140, altered viral tropism or anti-idiotypic PRO 140 antibodies, the cause of viral rebound is yet to be resolved. The determination of methods to select patients that may respond to PRO 140 monotherapy is clearly needed.

Limitations of the CD01 study include the high variability in the duration of HIV diagnosis, the extent of prior ART exposure in participants enrolled, the lack of baseline antiviral genotypic and/or phenotypic drug resistance profile for patients enrolled in this study. The ongoing CD01 Extension study is limited by population size, though the results show PRO 140 monotherapy has maintained HIV-1 RNA levels below 40 copies/mL for more than 3 years, and has exhibited an excellent long-term safety profile.

It is notable that other monotherapy strategies with protease inhibitors and recently with dolutegravir have failed.[19–21] This is further evidence that monotherapy in general is difficult and may be particularly so with agents directed at inhibiting the viral life cycle internally rather than entry inhibitors.

PRO 140 has a potential to address an unmet need for a simplified, long-acting, single-agent, maintenance regimen for HIV infection if host and/or virologic factors that predict treatment success on PRO 140 monotherapy can be identified. Currently, a large, multi-center, investigative Phase 2b/3 clinical study is underway to determine the cause for virologic rebound observed in the CD01 and CD01 Extension studies.

In summary, this trial showed that PRO 140 was potent enough and well enough tolerated that a substantial fraction of people could be suppressed on it alone for over three years. Over that time, there were no non-injection site AEs, no anti-PRO 140 antibodies detected, no selection of X4 virus, and even those who failed could universally be re-suppressed by returning to their original regimens. The fact that a good fraction of the participants could be suppressed so well with PRO 140 monotherapy for now over three years is strong support of the concept that this agent can become an important component of a long-acting combination regimen in this era when there is intensified interest in this approach for prevention and therapy. It could also be combined with multiple other agents including other monoclonals such as ibalizumab, broadly neutralizing anti-HIV antibodies and nano-formulated small molecules like cabotegravir and rilpivarine.

Disclosure statement

The research is sponsored by CytoDyn Inc. (Vancouver, WA, USA) and may lead to the development of a product. The authors have a financial and/or business interests in, are a consultant to, or receive funding from CytoDyn Inc. that may be affected by the research reported in the enclosed paper.

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Kazem Kazempour, PhD, is the President/CEO of Amarex Clinical Research, a global contract research organization, working with pharmaceutical, biotechnology, and medical device development companies since 1998. Kazempour has been involved in more than 200 clinical trials all around the world, starting inlate 1980. He has conducted presentations to the FDA and FDA advisory committees on more than 30 different clinical trials. Kazempour has authored numerous publications and technical reports. He has contributed and participated in hundreds of US Food and Drug Administration FDA meetings as well as other regulatory bodies around the world. During his 30-plus years of experience in biomedical research, Kazempour has conducted research activities in collaboration with the National Institutes of Health (NIH), within the pharmaceutical industry and at many educational institutions. During his tenure at the FDA, Kazempour also worked as a Senior Staff Fellow and Mathematical Statistician responsible for conducting independent statistical analyses for numerous clinical trials and reviewing clinical trials submissions and protocols. He has been a key contributor in the design, execution and approval of several drugs and devices. Kazempour has established, presented to and participated in many Data Safety Monitoring Boards for compounds within his area of expertise.

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In addition, the author works on multiple Integrated Summaries of Safety (ISS) and Integrated Summaries of Efficacy (ISE) reports that have been submitted to FDA and other regulatory agencies for drug approvals.

Denis Burger, PhD, was appointed a Director in February 2014, named Vice Chairman in August 2014 and Chief Science Officer in January 2016. He is a life sciences executive with over 30 years of extensive scientific, operational, and financial experience in the biotech industry. As CEO or chairman of several biotechnology companies, Burger has led numerous corporate financing transactions and public securities offerings and has experience leading R&D, GMP manufacturing and clinical development functional areas. Burger is currently a Director of Aptose Biosciences Inc., a cancer therapeutics, NASDAQ-listed company. Burger co-founded Trinity Biotech, a NASDAQ-listed diagnostic company, in June 1992, served as its Chairman from June 1992 to May 1995, and is currently lead independent director. Until March 2007, he was Chairman and Chief Executive Officer of AVI Biopharma Inc. (now Sarepta Therapeutics), a NASDAQ listed RNA therapeutics company. He was also a co-founder of Epitope Inc. (now Orasure Technologies, NASDAQ listed), serving as its Chairman from 1981 to 1990. Burger previously held a professorship in the

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Paul J. Maddon, PhD, is a biotechnology entrepreneur who founded Progenics Pharmaceuticals, Inc., a publicly traded biopharmaceutical company that develops new medicines in the areas of gastroenterology, oncology, and infectious diseases. He now serves as an advisor to several biotechnology and specialty pharmaceutical companies. Maddon is a molecular virologist and immunologist who has made major contributions to our understanding of viral entry and infection. In a series of landmark studies as a graduate student in the laboratory of Dr. Richard Axel, he isolated the gene encoding CD4 and demonstrated that CD4 serves as the primary receptor for entry HIV into immune system cells. While at Progenics, Maddon discovered that a co-receptor, CCR5, is also required for HIV entry. PRO 140, a humanized mAb to CCR5 designed to treat HIV infection discovered by Maddon, is now being tested in phase 3 clinical trials by CytoDyn Inc. Maddon has authored more than 50 peer-reviewed publications and served on the editorial board of Journal of Virology. At Columbia University, he received an MD from the College of Physicians and Surgeons and a PhD in biochemistry and molecular biophysics from the Graduate School of Arts and Sciences.

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