Safety, pharmacokinetics, and neutralisation activity of PGDM1400LS, a V2 specific HIV-1 broadly neutralising antibody, infused intravenously or subcutaneously in people without HIV-1 in the USA (HVTN 140/HPTN 101 part A): a first-in-human, phase 1 randomised trial

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Summary

Background: PGDM1400LS is a human monoclonal antibody targeting the HIV envelope V2 apex with a lysine-serine modification intended to enhance serum and tissue half-lives and is being considered for use in combination monoclonal antibody trials. We sought to test whether PGDM1400LS was safe and had favourable serum concentration, pharmacokinetics, and neutralising ability in healthy adults.

***Methods*:** HVTN 140/HPTN 101 part A is an open-label, dose escalation, first-in-human phase 1 trial of PGDM1400LS given intravenously or subcutaneously to healthy adults aged 18–50 years without HIV-1. The study enrolled participants at four sites in the USA, across five groups, each receiving one dose of PGDM1400-LS intravenously (group 1: 5 mg/kg; group 2: 20 mg/kg; and group 4: 40 mg/kg) or subcutaneously (group 3: 20 mg/kg; and group 5: 40 mg/kg). Participants in group 1 were enrolled sequentially without random assignment. Participants in groups 2 and 3 were block randomised and enrolled simultaneously after group 1 safety review. Groups 4 and 5 followed the same process, contingent on groups 2 and 3 safety review. The primary endpoints were safety and tolerability of PGDM1400LS, serum concentration of PGDM1400LS, and serum neutralising activity after single administration of PGDM1400LS. Serum PGDM1400LS concentrations collected at seven timepoints (day 0, day 3, day 6, day 28, day 56, day 112, and day 168) were assessed via an anti-idiotype binding assay and characterised via non-compartmental pharmacokinetic analysis. Serum neutralisation activity (ID_{80}) was assessed by a TZM-bl assay. The study is registered with ClinicalTrials.gov , NCT05184452.

Findings: Between Nov 15, 2021, and March 4, 2022, 15 participants were enrolled into the five study groups (three participants per group) with 6 months of follow-up. Ten of 15 participants were female, 14 of 15 participants were non-Hispanic, and 11 of 15 participants were White, with a median age of 27 years (range 24–47). PGDM1400LS was safe and well tolerated, with mild to moderate solicited symptoms. Serum concentrations showed dose proportionality by administration route, with peak concentrations observed immediately after intravenous infusion (range 95·7–727·4 μg/mL) or on day 6 after subcutaneous infusion (205·6–547·1 μg/mL). The median elimination half-life was 55 days (range 48–59), representing a 2-to-3-times increase versus parental PDGM1400. Estimated subcutaneous (*vs* intravenous) bioavailability was 50–60%. ID_{80} titres showed agreement with concentration-predicted ID_{80} titres, indicating maintenance of neutralisation activity in vivo.

***Interpretation*:** PGDM1400LS is a promising candidate for combination monoclonal antibody efficacy trials going forward.

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I

Introduction

Globally, there are an estimated 39·9 million people living with HIV, with 630 000 deaths in 2024.[1] Without an efficacious vaccine, medical options for HIV prevention include approved pre-exposure prophylaxis or intermittent oral pills, vaginal rings, and long-acting injectables, and investigational approaches, such as administration of monoclonal antibodies. Monoclonal antibodies that target the HIV envelope (Env) have been shown to prevent acquisition of HIV in non-human primate models,[2-9] providing proof of concept that broadly neutralising monoclonal antibodies can prevent HIV acquisition with sufficient antibody titres against neutralisation sensitive viruses.

Research in context

Evidence before this study

Multiple broadly neutralising monoclonal antibodies targeting different epitopes of the HIV envelope (Env) have been administered intramuscularly, intravenously, or subcutaneously to both people living with HIV as a potential therapeutic or curative strategy and those without HIV as a preventive measure. We did a systematic search from Oct 20, 2020, to June 23, 2021, in PubMed and ClinicalTrials.gov, of studies published in English, with the search terms "PGDM1400", "PGDM1400LS", and "VRC01", and assessed publications for quality evidence before and during study development. The recent Antibody Mediated Prevention (AMP) trials revealed that VRC01, a CD4 binding site targeting antibody, showed a prevention efficacy of 75% against transmitted strains susceptible to VRC01 (80% inhibitory concentration [IC_{80}] <1 µg/mL). Moreover, the serum monoclonal antibody concentration and neutralisation sensitivity of these susceptible strains were found to correlate with prevention efficacy. Data from the AMP trials also suggested that a combination of antibodies is needed for broad coverage of circulating HIV-1 strains to provide sufficient prevention efficacy. PGDM1400 is a broadly neutralising monoclonal antibody that binds to the V2 glycan region of Env with broad coverage, particularly to clade C strains (83% global coverage, median IC_{50} 0·003 µg/mL), and has a half-life of approximately 2–3 weeks in vivo. Introduction of an engineered lysine-serine substitution in the Fc region is known to extend half-life from 2–3 weeks to 2–3 months for other HIV monoclonal antibodies, enabling reduced dosing frequency. This first-in-human study tested different dosages of PGDM1400LS, administered either by an intravenous or subcutaneous route, for safety, pharmacokinetics, and neutralisation activity in vivo.

Added value of this study

Our trial showed that PGDM1400LS, one of very few HIV-1 Env V2 targeting monoclonal antibodies, was safe and well tolerated in the participant population, with mild to moderate reactogenicity and no observed antidrug antibodies after a single infusion. This monoclonal antibody retained neutralisation breadth and potency in vivo, and the lysine-serine modification of PGDM1400 increased the in vivo serum half-life by 2-to-3-times over that of the parental antibody, PGDM1400. The trial provides pharmacokinetic data upon which work in HIV therapy and prevention of HIV transmission in adults and children can be initiated.

Implications of all the available evidence

HVTN 140/HPTN 101 part A is part of a path to a prevention efficacy trial of a triple combination of broadly neutralising monoclonal antibodies that are directed towards the HIV-1 Env CD4 binding site, V2-apex, and V3-glycan epitopes. This trial complements HVTN 127/HPTN 087 (VRC07-523-LS), HVTN 130/HPTN 089 (PGDM1400, PGT121, 10-1074 alone or in combination with VRC07-523LS) and HVTN 136/HPTN 092 (PGT121.414LS alone or in combination with VRC07-523LS, first in human), a series of studies to evaluate safety and pharmacokinetics, and compare neutralisation

breadth and potency between monoclonal antibodies targeting different HIV-1 Env epitopes. Part B of HVTN 140/HPTN 101 used a triple broadly neutralising antibody combination (PGDM1400-LS, PGT121.414.LS, and VRC07-523LS) to lay the groundwork for a combination prevention efficacy trial.

The Antibody Mediated Prevention (AMP) trials showed that the CD4 binding site monoclonal antibody VRC01 could protect against HIV acquisition of susceptible strains, providing proof of concept for broadly neutralising monoclonal antibody protection.[10] Furthermore, monoclonal antibody concentration and 80% inhibitory concentration (IC_{80}) neutralisation titre correlated with prevention efficacy. Two key outcomes resulted from the AMP trials. The first outcome was development of a new biomarker termed predicted serum neutralisation 80% inhibitory dilution titre (PT_{80}).[11] The PT_{80} quantifies the neutralisation potency of antibodies in an individual's serum against an HIV-1 isolate and can be used to predict HIV-1 prevention efficacy. The second outcome was development of a panel of HIV-1 viruses isolated from AMP trial participants who acquired HIV during the trial.[12] This panel enables evaluation of the neutralisation breadth and potency for new monoclonal antibodies in development, including PGDM1400LS, against a panel of circulating clade B and C viruses.

Several monoclonal antibodies that are broader and more potent than VRC01 have been tested in non-human primates and early phase human trials. These monoclonal antibodies target different epitopes of Env, such as the CD4 binding site (VRC07-523LS and 3BNC117-LS, N6), V2 apex (PGDM1400 and CAP256-VRC26.25), V3 glycan (10-1074 and PGT121), and membrane proximal external region (10E8).13, 14 PGDM1400, a human monoclonal antibody that targets the Env V2 apex centred on N160 was shown to be protective in non-human primates and humanised mouse models. Additionally, PGDM1400 was shown to be safe and tolerable in phase 1 clinical trials,4, 15, 16 with 10–100-times increased potency, especially against clade C viruses, versus CD4 binding site antibodies, such as VRC01, and with an IC_{80} of 1 μg/mL against a wide panel of viruses.4, 17, 18 PGDM1400 prevented simian immunodeficiency virus transmission in a non-human primate model,4, 17 and has been shown to reduce HIV-1 RNA viral load in individuals with viraemia by up to 2·01 log_{10} copies per mL,[15] making it a promising candidate for future HIV-1 monoclonal antibody prevention and therapeutic strategies. Testing of the parental PGDM1400 monoclonal antibody in combination with PGT121 and VRC07-523-LS indicated no effect on pharmacokinetic parameters when the monoclonal antibody was administered alone or in combination. The half-life of PGDM1400 was estimated to be 25·4 days.[19] PGDM1400LS is an engineered derivative of PGDM1400 with lysine-serine amino acid substitutions to the Fc region designed to improve the in vivo antibody half-life in serum and tissue.[20] We present results from part A of a phase 1, randomised, first-in-human study of PGDM1400LS in adults without HIV-1, to foster design of future combination monoclonal strategies.

Methods

Study design and participants

The two-part HVTN 140/HPTN 101 trial, an open-label, dose escalation, first-in-human study, enrolled healthy adults without HIV aged 18–50 years who provided written informed consent. Eligibility criteria included good general health, as shown by medical history, physical examination, and screening laboratory tests; negative HIV-1 and HIV-2 test; willingness to receive HIV test results; willingness to discuss HIV acquisition likelihood; and committed to maintaining low likelihood of acquisition behaviour. Full eligibility criteria are listed in the appendix (p 78) . In part A, 15 participants were enrolled to one of five groups for dose escalation of intravenous or subcutaneous infusion of PGDM1400LS. Participants enrolled into group 1 (n=3) received 5 mg/kg intravenous PGDM1400LS at month 0. Following safety review of group 1, participants were enrolled into group 2 (20 mg/kg intravenous, n=3) and group 3 (20 mg/kg subcutaneous, n=3) and received PGDM1400LS at month 0. Following safety data review of groups 1–3, participants in group 4 (40 mg/kg intravenous, n=3) and group 5 (40 mg/kg subcutaneous, n=3) received PGDM1400LS at month 0. In part B, an additional 80 participants were enrolled to evaluate combination monoclonal antibody regimens after the safety of a single administration of PGDM1400LS was established in part A. Results from part B will be reported in a separate manuscript.

This paper reports results from part A for timely dissemination to inform HIV prevention and therapeutic efficacy trial planning. The study was approved by a single institutional review board for the four participating US university affiliated sites in part A. Sites were in Atlanta, Nashville, San Francisco, and Washington, DC.

PGDM1400LS was developed by the Vaccine Research Program of the National Institute of Allergy and Infectious Diseases (NIAID). PGDM1400LS was manufactured under Good Manufacturing Practice at Just-Evotec (Seattle, WA, USA) under contract to NIAID's Division of AIDS Vaccine Translational Research Branch. Drug product was filled and released at the NIAID Vaccine Research Center pilot plant, operated under contract by the Vaccine Clinical Materials Program, Leidos Biomedical Research, (Frederick, MD, USA). PGDM1400LS was provided at 100 mg/mL as 10 mL glass vials with a 4·75 mL fill volume.

The study is registered with ClinicalTrials.gov , NCT05184452 . The protocol is available in the appendix (p 13) .

Randomisation and masking

Enrolment in group 1 (intravenous 5 mg/kg) was restricted to one participant per day. Group 2 (intravenous 20 mg/kg) and group 3 (subcutaneous 20 mg/kg) enrolled participants simultaneously, and participants were randomly assigned after review of group 1 safety data. Group 4 (intravenous 40 mg/kg) and group 5 (subcutaneous 40 mg/kg) enrolled participants simultaneously, and participants were randomly assigned after review of group 2 and group 3 safety data. Participants' random assignment was computer generated. Participants and clinical research site staff were unmasked to participant group assignments. Laboratory staff were masked to treatment assignments within part A.

Procedures

PGDM1400LS was administered on the day of enrolment in part A via intravenous infusion over approximately 30–60 min or via subcutaneous infusion at a rate of about 15 mL/h per infusion site. Either electric constant rate (constant flow) or mechanical (constant pressure) pumps using one, two, or three infusion sites located at least 5·08 cm apart in the abdomen were used for subcutaneous administrations. In group 3 (subcutaneous 20 mg/kg), participants received total volumes between 10·2 mL and 35·0 mL administered in 27–65 min. In group 5 (subcutaneous 40 mg/kg), 22·1–35·0 mL were administered in 40–100 min. Safety assessments were done on all enrolled participants.

Participants remained in the clinic for observation for about 60 min after study product administration. During the observation period, participants filled out an acceptability questionnaire and were monitored for solicited local and systemic adverse events, including pain or tenderness, erythema or induration, infusion site pruritus, fever, urticaria, non-exertional tachycardia, malaise or fatigue, myalgias, arthralgias, chills, headache, nausea, generalised pruritus, facial flushing, unexplained diaphoresis, and non-exertional dyspnoea. Thereafter, the solicited adverse assessment period was 3 full days and participants documented adverse events with daily entries in a diary. Unsolicited adverse events were documented throughout the entire study period for each individual participant.

All adverse events were graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected version 2.1, July, 2017, [21] except unintentional weight loss, infusion site erythema or redness and infusion site induration or swelling, creatinine clearance, or estimated glomerular filtration rate (appendix p 3).

Data from brief physical examinations and laboratory testing (complete blood count with differential, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, urine dipstick, pregnancy testing, and HIV testing) were collected for safety monitoring at prespecified timepoints throughout the study (brief physical examination: day 0, day 3, day 6, day 28, day 56, day 112, and day 168; safety laboratory tests day 0, day 56, and day 168). The HVTN 140/HPTN 101 protocol safety review team and HVTN safety monitoring board monitored the safety reports throughout the study.

Neutralising antibodies against HIV-1 were measured as a function of reductions in Tat-regulated luciferase reporter gene expression in TZM-bl cells. [22,23] The assay measured serum neutralisation titres against an Env-pseudotyped virus (6540.v4.c1) sensitive to PGDM1400LS but resistant to VRC07.523LS and PGT121.414LS. The assay also measured serum neutralisation against an 11 virus panel (SHEP-T2: the sensitive HIV-1 Env panel, tier 2), which was selected to include the top two ranked viruses that are most sensitive to different broadly neutralising antibody classes from among 115 viruses from 76 participants in the AMP trial. A serum neutralisation titre was defined as the serum dilution that reduced relative luminescence units (RLUs) by 50% and 80% (ID_{50} and ID_{80}) relative to the RLUs in virus control wells (cells plus virus only) after subtraction of background RLU (cells only). The lower limit of detection was 10 for both ID_{50} and ID_{80} . Neutralisation ID_{50} and ID_{80} titres against virus 6540.v4.c1 were measured from specimens obtained at visits 2, 3, 4, 5, 6, 7, and 9, corresponding to before study product administration and 3 days, 6 days and 1, 2, 4, and 6

months after study product administration. Titres against the AMP Env-pseudotyped viruses were measured only at visit 6, corresponding to 2 months after study product administration, and results reported as IC_{50} s and IC_{80} s in µg/mL. Magnitude and breadth of heterologous tier 2 virus neutralisation was assessed using the same panel of 11 pseudotyped viruses mentioned previously.

Serum PGDM1400LS IgG concentrations were measured on a Bio-Plex instrument (Bio-Rad; Hercules, CA, USA) using a validated anti-idiotype pharmacokinetic assay as described previously. [24, 25] PGDM1400LS serum concentrations were calculated using 5-parameter logistic regression from a PGDM1400LS standard curve run on the same assay plate. The lower limit of quantification for PGDM1400LS is 78 ng/mL, and samples were titrated to obtain a concentration value within the linear range of the assay before reporting. All assays were done under Good Clinical Laboratory Practice guidance under the oversight of the Duke Quality Assurance for Vaccine Immunogenicity Programs.

The presence of anti-PGDM1400LS antibodies in serum was measured by a qualified anti-drug antibody screening assay, a bridging electrochemiluminescence assay, as previously described.[26,27] Samples were tested in duplicate along with a panel of anti-idiotype and negative controls and data accepted based on meeting pre-established criteria.

Outcomes

The primary clinical objective was to evaluate the safety and tolerability of PGDM1400LS. The primary endpoints were the frequency of local and systemic solicited adverse events, laboratory measures of safety, unsolicited adverse events, and serious adverse events recorded by clinicians at every visit. The primary laboratory objectives were evaluating serum concentrations and pharmacokinetics of PGDM1400LS and serum neutralising activity. Secondary outcomes were determining whether anti-drug antibodies were present.

Statistical analysis

Given the sample size of the study, descriptive analyses of the primary and secondary endpoints are reported. In supportive analyses, we used Lin's concordance correlation coefficient [28] to assess the concordance in two measurements. The concordance correlation coefficient is a composite measure of precision (Pearson's correlation coefficient) and accuracy (bias).

Non-compartmental pharmacokinetic analyses of PGDM1400LS serum concentrations were done on the modified intention-to-treat cohort that included all enrolled participants in part A who received study product. Individual concentration profiles were summarised by computing the area under the time–concentration curve (AUC) from day 0 to the day 168 visit, using the trapezoidal method applied to untransformed serum concentrations, and then dose-normalised by dividing the statistic by dose level in mg/kg (dose-normalised $AUC_{0–168}$, kg/L × day). The observed trough was measured at approximately 168 days after study product administration. The terminal half-life was estimated based on the terminal elimination rate constant, calculated as the slope of the log-linear portion (28–168 days after study product administration) of the time–concentration curve. Individual-level linear

regression models were fitted for log-transformed concentrations over time; the coefficient of time from each participant's fit (slope) was the elimination rate constant. The terminal half-life was calculated as the absolute value of Ln(2) divided by the elimination rate constant. Clearance was computed as the administrated amount of PGDM1400LS divided by AUC $_{0\text{-inf}}$ (the AUC from day 0 to infinity, calculated as AUC $_{0–168}$ + abs [observed trough/elimination rate constant]). The volume of distribution was computed as the absolute value of clearance divided by the elimination rate constant. Additionally, bioavailability was estimated by the median dose-normalised AUC $_{0–168}$ of subcutaneous administration divided by that of intravenous administration. All analyses were done using SAS version 9.4 and R 4.0.4.

Role of the funding source

The funder has medical officer representatives on the protocol team who had input into the study design, data interpretation, and writing of the report.

Results

Between Nov 15, 2021, and March 4, 2022, 15 participants were enrolled into the five study groups (three participants per group) with 6 months of follow-up (figure 1). Follow-up visits were completed on Aug 22, 2022. Ten of 15 participants were female, 14 of 15 participants were non-Hispanic, and 11 of 15 participants were White, with a median age of 27 years (range 24–47; table 1).

All solicited local and systemic symptoms were mild to moderate in severity (table 2). Solicited local symptoms reported included mild pain or tenderness in three of 15 participants (one participant in group 2, one participant in group 3, and one participant in group 5); mild erythema or induration in two participants (one participant in group 3 and one participant in group 5) and moderate erythema or induration in one participant in group 5; and mild infusion site pruritus in two participants (one participant in group 3 and one participant in group 5). Solicited local symptoms resolved within 2–4 days. Overall, solicited local symptoms were more commonly reported in the subcutaneous infusion groups (groups 3 and 5; table 2).

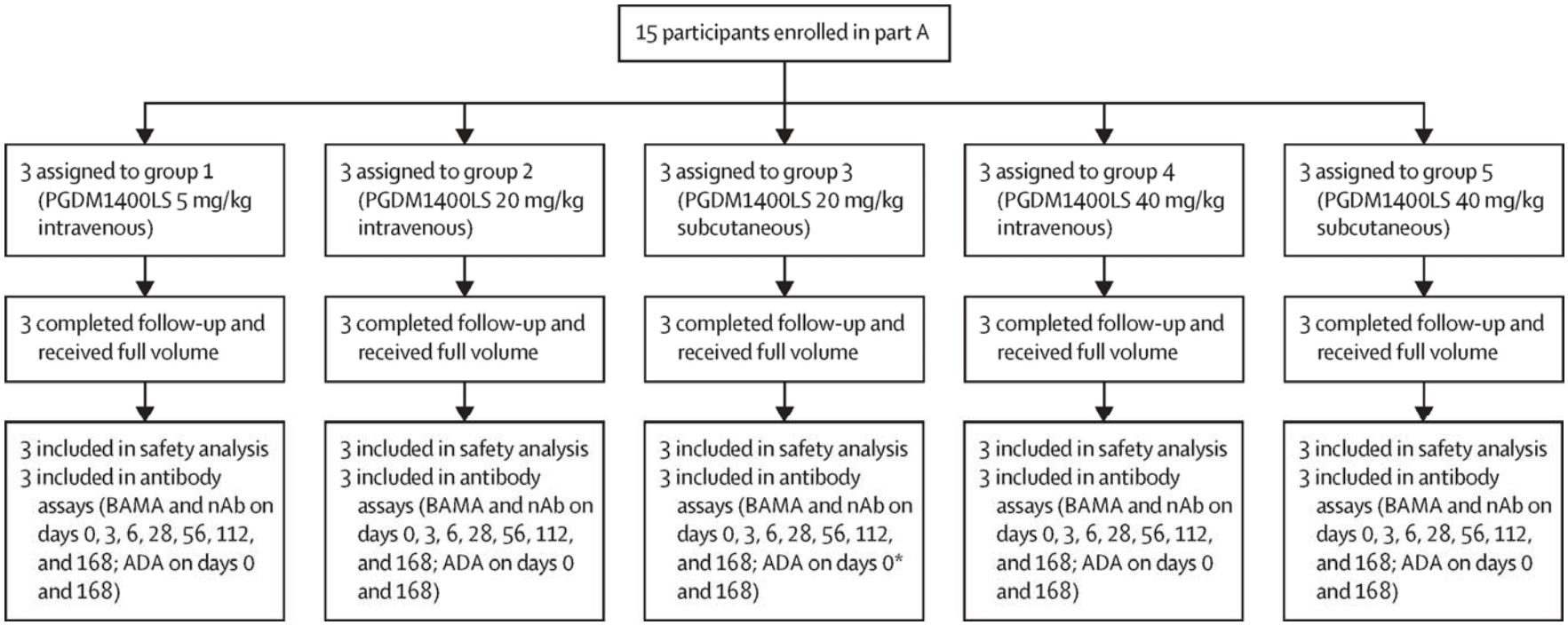

Figure 1. Trial profile

ADA=anti-drug antibody. BAMA=binding antibody multiplex assay. nAb=neutralising antibody. *Two participants had ADA on day 0.

Table 1. Participant demographics at enrolment in HVTN 140/HPTN 101 part A

	Group 1 (5 mg/kg intravenous; n=3)	Group 2 (20 mg/kg intravenous; n=3)	Group 3 (20 mg/kg subcutaneous; n=3)	Group 4 (40 mg/kg intravenous; n=3)	Group 5 (40 mg/kg subcutaneous; n=3)	Total (n=15)
Sex						
Male	1	1	1	1	1	5
Female	2	2	2	2	2	10
Ethnicity						
Hispanic or Latino (or Latina)	0	0	0	0	1	1
Not Hispanic or Latino (or Latina)	3	3	3	3	2	14
Race						
White	1	3	2	3	2	11
Black or African American	1	0	0	0	0	1
Asian	0	0	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0	0
Multiracial	1	0	1	0	0	2
Other	0	0	0	0	1	1
Age, years						
21–30	1	3	2	2	1	9
31–40	2	0	1	1	1	5
41–50	0	0	0	0	1	1
Median (range)	36 (25–38)	27 (24–27)	27 (25–34)	26 (24–33)	33 (29–48)	27 (24–48)
Weight, kg						
Median (range)	72·0 (57·7–95·1)	75·0 (64·3–80·5)	75·0 (48·1–76·2)	67·0 (65·2–68·3)	75·0 (54·5–89·8)	75·0 (48·1–95·1)

Data are n, unless otherwise indicated. No participants were younger than 20 years or older than 50 years.

Table 2. Maximum local and systemic solicited adverse events by treatment group

	Group 1 (n=3)	Group 2 (n=3)	Group 3 (n=3)	Group 4 (n=3)	Group 5 (n=3)
Local					
Erythema or induration					
None	3	3	2	3	1
Mild	0	0	1	0	1
Moderate	0	0	0	0	1
Erythema or redness					
None	3	3	2	3	1
Mild	0	0	1	0	1
Moderate	0	0	0	0	1
Induration or swelling					
None	3	3	2	3	1
Mild	0	0	1	0	1
Moderate	0	0	0	0	1
Injection site pruritus					
None	3	3	2	3	2
Mild	0	0	1	0	1
Pain or tenderness					
None	3	2	2	3	2
Mild	0	1	1	0	1
Systemic					
Headache					
None	3	1	2	2	2
Mild	0	1	1	1	1
Moderate	0	1	0	0	0
Malaise or fatigue					
None	3	1	3	2	3
Mild	0	2	0	1	0
Maximum systemic symptoms					
None	2	1	2	2	2
Mild	1	1	1	1	1
Moderate	0	1	0	0	0
Nausea					
None	2	3	3	3	3
Mild	1	0	0	0	0

Data are n. Only the symptoms that participants exhibited are included in the table.

Reported solicited systemic symptoms included mild malaise or fatigue in three participants (two participants in group 2 deemed related to study product and one participant in group 4 deemed not related to study product); study product-related mild nausea in one participant in group 1; mild headache in four participants (one participant in group 2 and one participant in group 3 deemed related to study product and one participant in group 4 and one participant in group 5 deemed not related to study product); and study product-related moderate headache in one participant in group 2. Two participants had three solicited symptoms that were deemed to be not related to study product. One participant (in group 4) reported mild malaise or fatigue and headache, which were attributed to caffeine withdrawal,

dehydration, and work. The other participant (in group 5) had a mild headache and reported no alternate cause. All solicited systemic symptoms resolved within 2 days.

Eight participants reported a total of 11 unsolicited adverse events, of which one was deemed related to study product in a participant from group 5, who received a single subcutaneous infusion at 40 mg/kg. The participant reported no pre-existing dermatological, allergic, or autoimmune conditions but had a delayed onset of severe (grade 3) skin erythema, with a diameter of approximately 15 cm at the subcutaneous infusion site in the lower abdomen beginning on day 7 after study product administration. The erythema was accompanied by oedema without induration in the distribution of the infusion and extending laterally beyond the infusion sites. Moreover, the participant reported localised itching that lasted 4 days and resolved without any treatment. This event gradually improved and spontaneously resolved with no sequelae after 22 days. The protocol safety review team and safety monitoring board reviewed this adverse event and determined it was safe to proceed with administration of PGDM1400LS subcutaneous infusions to other study participants, as this event was a localised site reaction with no systemic symptoms. The remaining five participants who received subcutaneous infusions at 20 mg/kg (group 3) or 40 mg/kg (group 5) tolerated the infusions and did not report any unsolicited adverse event deemed study product-related.

Most non-study product-related unsolicited adverse events were reported in the infections category. All non-related unsolicited adverse events were mild or moderate in severity. There were no serious adverse events or infusion-related reactions reported in part A of the study. Infusion-related reactions were defined as more than one sign or symptom present during or after infusion, in the absence of anaphylaxis, and the constellation of these signs or symptoms being deemed to be an antibody reaction by the clinical research site investigator of record. There were no study pauses due to safety concerns and no partial volume infusions were administered to any of the participants.

All participants in part A of the study completed acceptability questionnaires within an hour after study product administration to assess their views on aspects of administration, including discomfort and willingness to receive product via a specific administration route. Ten of 15 participants did not report any discomfort, including the three participants in group 3 and one participant in group 5. Among the five participants who had discomfort (one in group 1, two in group 2, and two in group 5), four of five were mildly uncomfortable and one reported moderate discomfort (one participant in group 5). The participant who later had delayed onset severe site skin rash and itching after subcutaneous infusion initially reported acceptable mild discomfort after the infusion. All five participants assessed the level of discomfort as acceptable. Additionally, 13 of 15 participants, including the participant who reported the delayed onset severe subcutaneous infusion site rash, were willing to receive intravenous or subcutaneous infusion to protect themselves from getting a serious disease, such as HIV, if they were at high likelihood for acquisition. These same participants also indicated that they would recommend receiving an intravenous or subcutaneous infusion to a friend who was susceptible to HIV.

Serum concentrations from all 15 participants were measured with a validated anti-idiotype pharmacokinetic assay [26] and analysed via non-compartmental analysis to avoid assumptions about how the drug distributes and clears the body. We plotted serum concentrations of

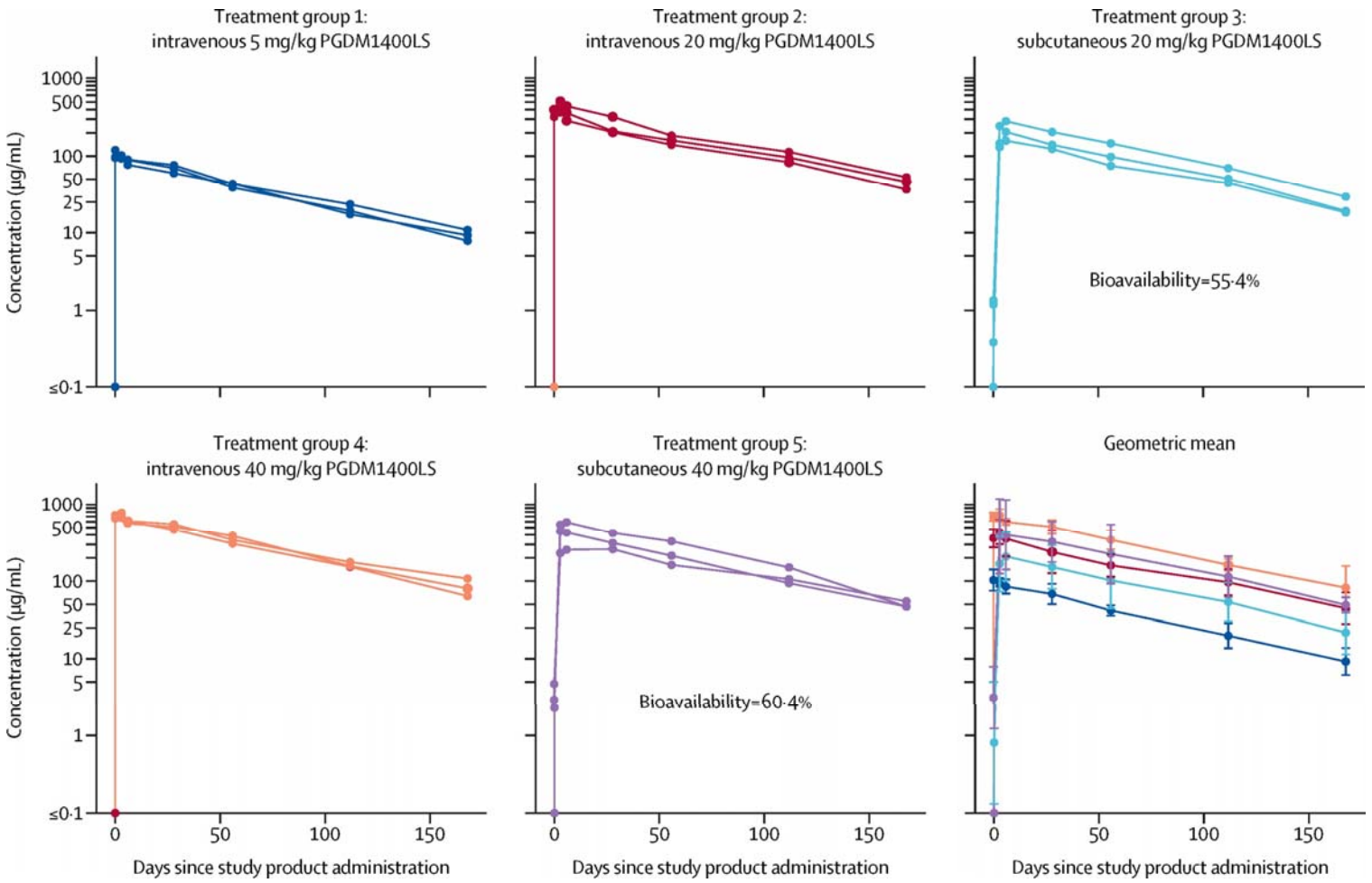

Figure 2. Serum concentration geometric means by treatment group and target day after study product administration

Vertical lines in the geometric mean graph indicate SE of the mean. Bioavailability between subcutaneous and intravenous at same dose comparisons are shown in the respective panels.

PGDM1400LS measured in individual study participants as a function of target day (after study product administration) by group (figure 2 ; appendix p 4). Peak serum concentrations were observed immediately (within 30–60 min) after infusion for participants receiving intravenous administration (group 1 median 95·7 μg/mL; group 2 median 432·6 μg/mL; group 4 median 727·4 μg/mL) or on study day 6 for participants in the subcutaneous administration groups (group 3 median 205·6 μg/mL; group 5 median 547·1 μg/mL). As expected, peak concentrations of PGDM1400LS were highest in the intravenous 40 mg/kg group (group 4). The analysis of peak concentrations (without restriction to a specific study day) and dose-normalised $AUC_{0–168}$ showed dose proportionality of the pharmacokinetics for both routes of administration (appendix p 6). The relationship between peak concentration and administered dose was linear (R^2 =0·96; p<0·0001), further evidenced by the absence of association between the dose-normalised concentration and dose within the intravenous groups (groups 1, 2, and 4).

The median dose-normalised $AUC_{0–168}$ for the intravenous groups was 1231 kg/mL × day. The median dose-normalised $AUC_{0–168}$ for the subcutaneous groups was 697 kg/L × day for group 3 and 761 kg/L × day for group 5 (appendix p 4). The corresponding estimated bioavailability of subcutaneous (*vs* intravenous) administration was 57–62%.

Median elimination half-life across all groups was 55 days, a 2-to-3-times increase compared with previous studies of PDGM1400 lacking the lysine-serine modifications. [15] Specifically, median elimination half-life was 47·9 days in group 1, 58·8 days in group 2, 51·6 days in group 3, 55·2 days in group 4, and 52·3 days in group 5 (appendix p 4). Clearance and volume of distribution had similar distributions in the intravenous groups and subcutaneous groups. The median clearances of intravenous groups were all approximately 0·05 L/day and the median volumes of distribution were 3·8–4·5 L. The median clearance of subcutaneous groups was approximately 0·07 L/day and the median volumes of distribution were 5·0 L in group 3 and 4·8 L in group 5.

At post study product administration timepoints, high rates of detectable ID_{50} and ID_{80} titres (>10) were observed to the PGDM1400LS-sensitive virus 6540.v4.c1 in all groups. Neutralisation titres became undetectable only in group 1 at month 6 for ID_{80} . ID_{50} and ID_{80} titres for most participants reached their peak at day 3 after study product administration, then gradually declined up to 6 months after study product administration. Group 1 had the lowest neutralisation titres, groups 2 and 3 had higher neutralisation titres, and groups 4 and 5 had the highest neutralisation titres (appendix pp 7–8). For groups with the same dose but different administration routes (intravenous *vs* subcutaneous), responses in the intravenous groups reached the peak more quickly than in the subcutaneous groups. The response differences between intravenous and subcutaneous groups then narrowed gradually up to 2 months after study product administration and increased at months 4 and 6 (appendix pp 7, 8).

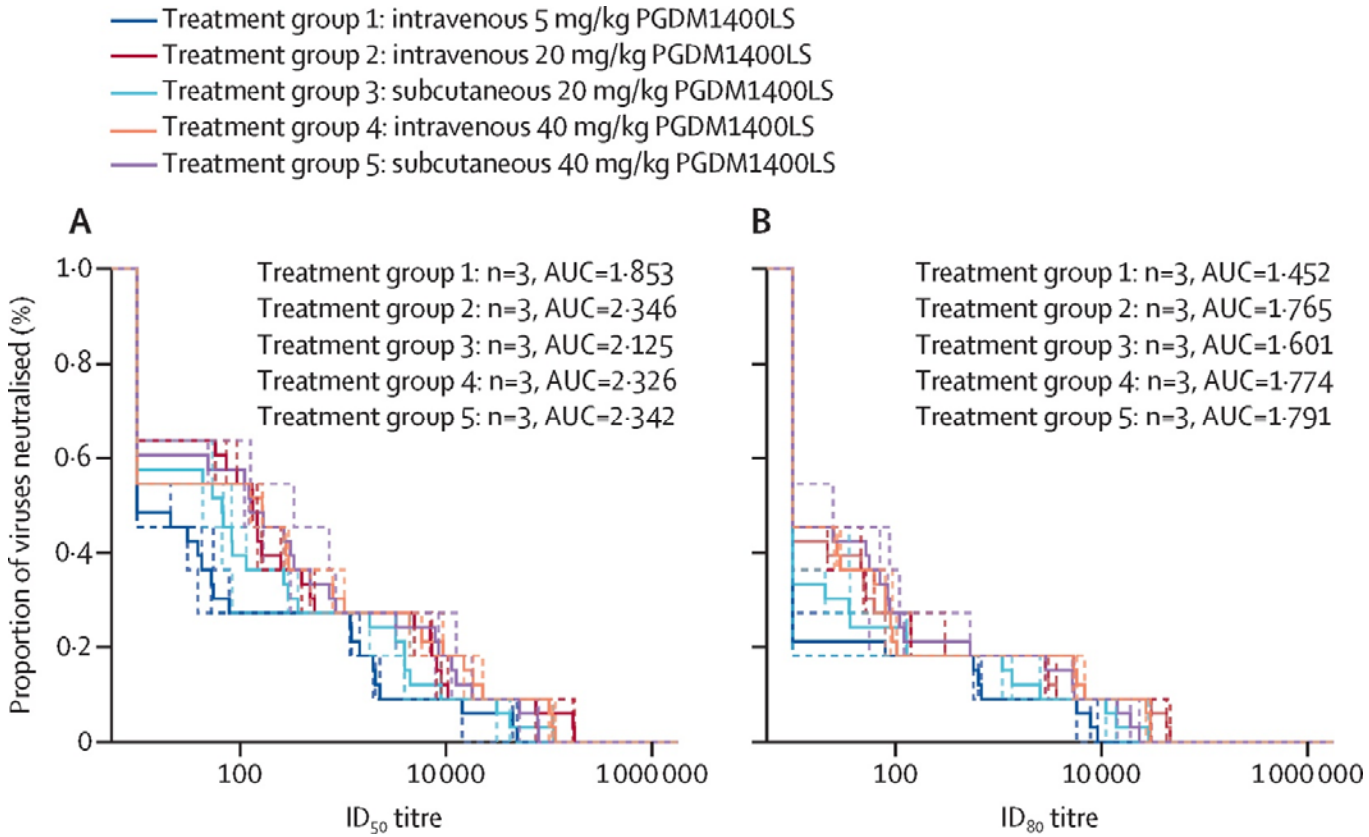

Figure 3. Magnitude and breadth curves for PGDM1400LS neutralising activity

ID_{50} (A) and ID_{80} (B) values at 2 months after study product administration. A panel of 11 pseudoviruses were tested for neutralisation activity: H703_0472_030s, H703_2117_110_RE_e2A10s, H703_2304_150_RE_cs, H703_2805_080Es, H704_0128_220_RE_pb001_s, H704_0445_180_RE_con_s, H704_0855_080_EsN, H704_0907_130sN, H704_1180_070EsN, H704_1528_240_RE_pblib_001_s, and H704_1535_030sN. AUC=area under the curve.

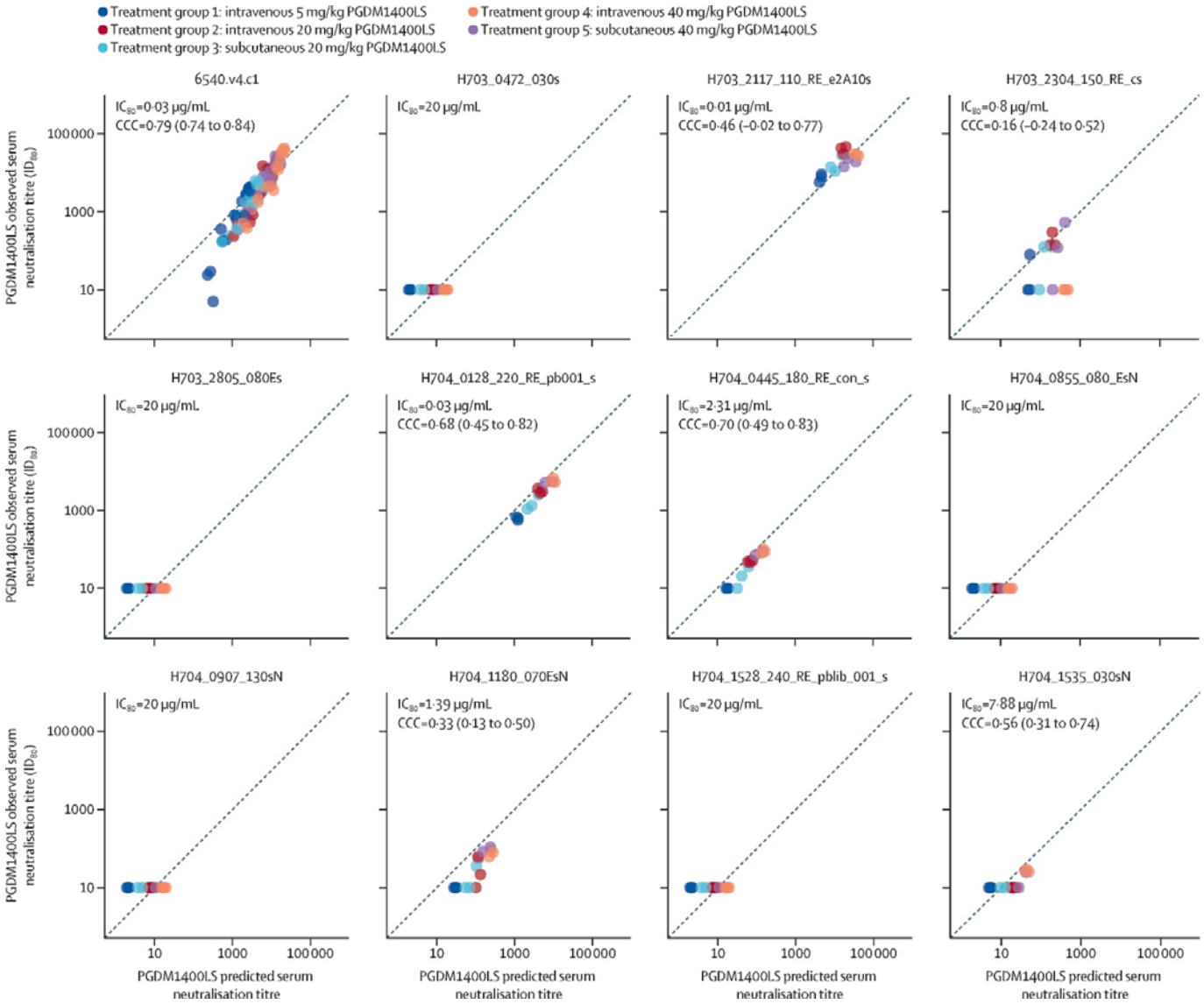
Treatment group 1: intravenous 5 mg/kg PGDM1400LS
Treatment group 2: intravenous 20 mg/kg PGDM1400LS
Treatment group 3: subcutaneous 20 mg/kg PGDM1400LS
Treatment group 4: intravenous 40 mg/kg PGDM1400LS
Treatment group 5: subcutaneous 40 mg/kg PGDM1400LS
6540.v4.c1
IC80=0·03 µg/mL
CCC=0·79 (0·74 to 0·84)
H703_0472_030s
IC80=20 µg/mL
H703_2117_110_RE_e2A10s
IC80=0·01 µg/mL
CCC=0·46 (−0·02 to 0·77)
H703_2304_150_RE_cs
IC80=0·8 µg/mL
CCC=0·16 (−0·24 to 0·52)
H703_2805_080Es
IC80=20 µg/mL
H704_0128_220_RE_pb001_s
IC80=0·03 µg/mL
CCC=0·68 (0·45 to 0·82)
H704_0445_180_RE_con_s
IC80=2·31 µg/mL
CCC=0·70 (0·49 to 0·83)
H704_0855_080_EsN
IC80=20 µg/mL
H704_0907_130sN
IC80=20 µg/mL
H704_1180_070EsN
IC80=1·39 µg/mL
CCC=0·33 (0·13 to 0·50)
H704_1528_240_RE_pblib_001_s
IC80=20 µg/mL
H704_1535_030sN
IC80=7·88 µg/mL
CCC=0·56 (0·31 to 0·74)
PGDM1400LS observed serum neutralisation titre (ID80)
PGDM1400LS predicted serum neutralisation titre
10
1000
100000

Figure 4. Observed versus predicted serum neutralisation titre for PGDM1400LS

Values in the upper left corner of each plot correspond to IC_{80} (µg/mL) and CCC agreement values with 95% CIs in parentheses. Observed titres below the lower limit of quantification (20 µg/mL) are set to lower limit of quantification divided by two. The CCC is not computed when data variability is low. Neutralisation against 6540.v4.c1 was measured at all study visits and combined for the CCC calculation. Neutralisation against the Antibody Mediated Prevention panel was measured at 2 months after study product infusion. CCC=concordance correlation coefficient.

The neutralisation activity of the parental monoclonal antibody PGDM1400 was measured against a panel of viruses isolated from placebo recipients who acquired HIV during the AMP trials (appendix pp 9–10), [12] confirming increased coverage and potency against circulating clade C viruses versus circulating clade B viruses. [15] Additionally, the neutralisation activity of PGDM1400LS was generally similar to PGDM1400 neutralisation activity against a PGDM1400LS-sensitive virus (6540.v4.c1) and the subset of 11 AMP panel viruses (appendix pp 9–10). The panel was intended to maximise the ability to detect low levels of heterologous tier 2 virus neutralisation, and is not intended to closely approximate the natural diversity of contemporary viruses. Participants in the 20 mg/kg and 40 mg/kg intravenous groups had the highest magnitude and breadth of ID_{50} and ID_{80} neutralising activity 2 months after study product administration (figure 3). In the current study, PGDM1400LS was measured against a subset of clade B and clade C viruses with varying levels of sensitivity to PGDM1400 in vitro (appendix p 5). Observed ID_{80} values for PGDM1400LS tested against 6540.v4.c1 and a subset of 11 AMP panel clade B and clade C viruses (appendix p 5) were consistent with PT_{80} values for PGDM1400-sensitive viruses (figure 4 ; appendix p 12), indicating the maintenance of neutralisation activity in vivo after passive intravenous or subcutaneous administration.

Samples were tested for the presence of antidrug antibodies at baseline (pre-infusion) and at month 6 post-infusion. No antidrug antibodies were observed in any participants at either timepoint (appendix p 11).

Discussion

The current study was the first-in-human trial of PGDM1400LS, a V2-apex-targeting antibody engineered with a lysine-serine modification, which is under consideration for use in combination monoclonal broad neutralising antibody HIV-1 prevention, therapeutic, and cure strategies. Data from HVTN 140/HPTN 101 part A indicated that PGDM1400LS administered intravenously or subcutaneously at 5 mg/kg, 20 mg/kg, or 40 mg/kg was safe and well tolerated. Additionally, participants reported that intravenous and subcutaneous infusions were acceptable and that they would recommend these routes of administration for future delivery of prevention modalities for HIV. One participant, who received a 40 mg/kg subcutaneous infusion, had a delayed onset infusion site erythema lasting about 3 weeks, during which the participant remained stable before the erythema resolved without treatment. Mild pain or tenderness was observed in the subcutaneous infusion groups at lower rates than reported from subcutaneous injection in other monoclonal antibody clinical trials. This finding could be related to a slower rate of subcutaneous administration by infusion versus injection. [27,29] These data build upon the phase 1 trial HVTN 130/HPTN 089, which tested several combination antibody regimens with monoclonal antibodies targeting different epitopes of the HIV envelope, including PGDM1400, the parent version of PGDM1400LS. Results of HVTN130/HPTN089 showed that dual and triple combinations of PGT121, PGDM1400, 10-1074, and VRC07-523LS were safe and did not affect individual broadly neutralising antibody pharmacokinetic characteristics, further indicating that broadly neutralising monoclonal antibodies with these specificities are good candidates for future combination prevention, treatment, and cure strategies.[19] As expected, introduction of the lysine-serine modification into the Fc region increased the elimination half-life of PGDM1400LS to 47·9–58·8 days from 20·8–25·4 days for the parental PGDM1400 monoclonal

antibody.[15, 19] Engineered antibodies with increased half-life are crucial to enable decreased dosing frequency, reduced costs, and maintenance of potentially protective serum concentrations over time. The median half-life of 51·6 days for PGDM1400LS allows for administration every 6 months [30] and is compatible with the half-life of other lysine-serine-engineered monoclonal antibodies under consideration for combination broadly neutralising monoclonal antibody cocktails, including PGT121.414.LS (half-life around 71 days) and VRC07-523-LS (half-life around 53 days). [30, 31] PGDM1400LS showed favourable pharmacokinetics via intravenous administration, with modest bioavailability when delivered via subcutaneous administration. Although subcutaneous administration might be advantageous due to relative ease of delivery and potentially reduced product costs with sufficiently high bioavailability, use of subcutaneous delivery methods in adults for current monoclonal antibodies would necessitate additional development in antibody delivery technologies before broader implementation to increase antibody availability and coverage. However, subcutaneous delivery methods are under consideration for neonates and infants due to decreased amount of antibody based on weight to achieve similar serum levels. [32,22]

The parental PGDM1400 monoclonal antibody is a broad and potent broadly neutralising antibody, neutralising 83% of a panel of 106 cross-clade pseudoviruses at a median IC_{50} of 0·003 μg/mL. [17] Testing against a panel of viruses isolated from AMP placebo recipients also indicated that PGDM1400 showed relatively high coverage against clade C viruses (71–75%), with less resistance to currently circulating strains than a similar V2 targeting monoclonal antibody, CAP256.25, [12] further supporting the use of PGDM1400 in future combination monoclonal antibody cocktails for HIV prevention in sub-Saharan Africa. Additionally, the dynamic range in IC_{50} and IC_{80} values for clade B and C for PGDM1400 was similar. We observed excellent concordance between PGDM1400 and PGDM1400LS assayed against 43 clade B viruses and 12 sensitive HIV-1 Env panel tier 2 viruses. Therefore, we expect little effect of the lysine-serine mutation on neutralisation activity against clade C viruses.

Limitations of this study include a small sample size of 15 participants, with additional evaluation needed in larger populations, including the ongoing analysis of PGDM1400LS as part of a combination regimen in HVTN 140/HPTN 101 part B. Additionally, part A was done at clinical trial sites in the USA. HVTN 140/HPTN 101 part B was done in the USA, Kenya, South Africa, and Zimbabwe and will provide additional data supporting future trials. Importantly, data from HVTN 140/HPTN 101 part A can now be applied to modelling and predicting PT_{80} for future combination broadly neutralising antibody trial design, including future infant and paediatric trials.In conclusion, data from HVTN 140/HPTN 101 part A show that PGDM1400LS is safe and well tolerated, with favourable pharmacokinetics and HIV-1 neutralisation breadth, including against clade C viruses, for consideration as part of a combination broadly neutralising antibody regimen. Additionally, the observed pharmacokinetics and neutralisation profile of PGMD1400LS in vivo were as expected, indicating no loss of activity in vivo and suitability for consideration in future trials. These data add to the body of knowledge of pharmacokinetics for V2-specific HIV-targeting broadly neutralising monoclonal antibodies and allow for rapid feedback and iteration of combination monoclonal antibody efficacy trial design.

Contributors

KES: provided supervision, designed and evaluated experimental approaches, investigation, writing—original draft. CAP: provided supervision, investigation, contributed to the original draft, writing—review and editing. CY: curated the data, data visualisation, contributed to the original draft, writing—review and editing. MDM: writing—original draft, data visualisation, writing—review and editing. STK: conceptualisation, supervision, writing—review and editing. TG: conceptualisation, supervision, investigation, writing—review and editing. JH: provided supervision, methodology, formal analysis, data curation, writing—review and editing. LZ: curated the data, data visualisation, writing—review and editing. MY: provided supervision, designed and evaluated experimental approaches, writing—review and editing. HSp: writing—review and editing. JBD: design of experimental approaches (pharmacokinetic sampling scheme), writing—review and editing. MA: investigation, writing—review and editing. EP-M: provided clinical laboratory input. BD: investigation, writing—review and editing. IT: investigation, writing—review and editing. LP-B: investigation, writing—review and editing. FG: curated the data, data visualisation, writing—review and editing. SAK: provided supervision, investigation, writing—review and editing. HSc: provided supervision, investigation, writing—review and editing. NNM: investigation, writing—review and editing. MJM: funding acquisition, writing—review and editing. MP: product development or manufacturing, writing—review and editing. DHB: product development or manufacturing, writing—review and editing. YH: investigation, writing—review and editing. DM: provided supervision, investigation, writing—review and editing. GDT: provided supervision, designed and evaluated experimental approaches, funding acquisition, writing—review and editing. LC: funding acquisition, conceptualised the study, writing—review and editing. MSC: funding acquisition, writing—review and editing. SM: provided supervision, designed and evaluated experimental approaches, investigation, writing—review and editing. MS: provided supervision, designed and evaluated experimental approaches, investigation, writing—review and editing. CFK: provided supervision, implemented clinical trial, investigation, writing—original draft, writing—review and editing. MT: writing—review and editing. MEA: provided supervision, designed and evaluated experimental approaches, writing—review and editing. VCB: provided supervision, writing—review and editing. JAW: investigation, writing—review and editing. ST: conceptualisation, supervision, writing—review and editing. AT: supervision, writing—review and editing. YH, CY, CAP, SM, MS, and CFK had full access to and verified all the data in the study. KES, CY, CAP, SM, MS, and CFK had final responsibility for the decision to submit for publication.

Data sharing

De-identified participant-level and aggregate-level data will be made publicly available via the Atlas Science Portal at https://atlas.scharp.org/project/HVTN%20Public%20Data/begin.view.

Declaration of interests

CFK receives research grant support from her institution from Moderna, Novavax, Humanigen, Gilead, and ViiV Healthcare. YH reports funding to her institution from National Institutes of Health (NIH) and WHO and sits on the advisory board of Worcester HIV Vaccine. JH reports funding from the NIH to his institution. HSc reports serving on the HIV Vaccine

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